1267594

THE UNITED STATES OF AMERICA

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December 30, 2004

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RELATED PCT APPLICATION NUMBER: *PCT/US04/35513*

Certified by

Jon W Dudas

Acting Under Secretary of Commerce
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Modified PTO/SB/16 (6-95)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

Docket Number	P-15439	Type a plus sign (+) inside this box -->	+

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE NAME	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
YEE	YING	KWONG	CARMEL, INDIANA
LU	JIANLIANG		FISHERS, INDIANA
NAGPAL	SUNIL		CARMEL, INDIANA
MA	TIANWEI		CARMEL, INDIANA
LINEBARGER	JARED	HARRIS	INDIANAPOLIS, INDIANA
JONES	CHARLES	DAVID	INDIANAPOLIS, INDIANA
GAJEWSKI	ROBERT	PETER	INDIANAPOLIS, INDIANA

TITLE OF THE INVENTION (280 characters max)

Vitamin D Receptor Modulators

CORRESPONDENCE ADDRESS

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

25885
PATENT TRADEMARK OFFICE

STATE	IN	ZIP CODE	46206-6288	COUNTRY	USA

ENCLOSED APPLICATION PARTS (*check all that apply*)

- [X] Specification — Number of pages: 187
- [ ] Small Entity Statement
- [ ] Drawing(s) — Number of Sheets:
- [ ] Other (Specify)

METHOD OF PAYMENT (*check one*)

- [ ] A check or money order is enclosed to cover the Provisional filing fees
- [X] The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 05-0840

PROVISIONAL FILING FEE AMOUNT ($): $160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- [X] No.
- [ ] Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,
SIGNATURE Roger S. Benjamin Date 20/ 11 / 2003 (20 NOVEMBER 2003)

TYPED or PRINTED NAME Roger S. Benjamin REGISTRATION NO. (*if appropriate*) 27,025

- [ ] Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FOR PATENT FILING ONLY

"Express Mail" mailing label number EV 357404867 US Date of Deposit 20 November 2003
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA, 22313-1450.

QUEEN THOMAS
Printed Name

Queen Thomas
Signature

VITAMIN D RECEPTOR MODULATORS

BACKGROUND OF THE INVENTION

Vitamin D_3 Receptor (VDR) is a ligand dependent transcription factor that belongs to the superfamily of nuclear hormone receptors. The VDR protein is 427 amino acids, with a molecular weight of ~50 kDa. The VDR ligand, 1α,25-dihydroxyvitamin D3 (the hormonally active form of Vitamin D) has its action mediated by its interaction with the nuclear receptor known as Vitamin D receptor ("VDR"). The VDR ligand, 1α,25-dihydroxyvitamin D3 ($1\alpha,25(OH)_2D_3$) acts upon a wide variety of tissues and cells both related to and unrelated to calcium and phosphate homeostasis.

The activity 1α,25-dihydroxyvitamin D3 in various systems suggests wide clinical applications. However, use of conventional VDR ligands is hampered by their associated toxicity, namely hypercalcemia (elevated serum calcium). Currently, $1\alpha,25(OH)_2D_3$, marketed as Rocaltrol® pharmaceutical agent (product of Hoffmann-La Roche), is administered to kidney failure patients undergoing chronic kidney dialysis to treat hypocalcemia and the resultant metabolic bone disease. Other therapeutic agents, such as Calcipotriol® (synthetic analog of $1\alpha,25(OH)_2D_3$) show increased separation of binding affinity on VDR from hypercalcemic activity.

Recently, chemical modifications of $1\alpha,25(OH)_2D_3$ have yielded analogs with attenuated calcium mobilization effects (R. Bouillon et. al., Endocrine Rev. 1995, 16, 200-257). One such analog, Dovonex ® pharmaceutical agent (product of Bristol-Meyers Squibb Co.), is currently used in Europe and the United States as a topical treatment for mild to moderate psoriasis (K. Kragballe et. al., Br. J. Dermatol. 1988, 119, 223-230).

Other Vitamin D_3 mimics have been described in the publication, Vitamin D Analogs: Mechanism of Action of Therapeutic Applications, by Nagpal, S.; Lu, J.; Boehm, M. F., Curr. Med. Chem. 2001, 8,.1661-1679.

Although some degree of separation between the beneficial action and calcium raising (calcemic) effects has been achieved with these VDR ligands, to date the separation has been insufficient to allow for oral administration to treat conditions such as osteoporosis, cancers, leukemias, and severe psoriasis.

One example of a major class of disorder that could benefit from VDR mediated biological efficacy in the absence of hypercalcemia is osteoporosis. Osteoporosis is a systemic disorder characterized by decreased bone mass and microarchitectural deterioration of bone tissue leading to bone fragility and increased susceptibility to fractures of the hip, spine, and wrist (World Health Organization WHO 1994). Osteoporosis affects an estimated 75 million people in the United States, Europe, and Japan.

Within the past few years, several antiresorptive therapies have been introduced. These include bisphosphonates, hormone replacement therapy (HRT), a selective estrogen receptor modulator (SERM), and calcitonins. These treatments reduce bone resorption, bone formation, and increase bone density. However, none of these treatments increase true bone volume nor can they restore lost bone architecture.

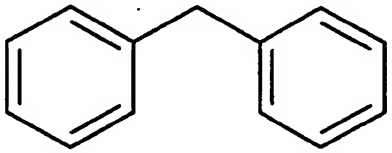
Synthetic VDR ligands with reduced calcemic potential have been synthesized. For example, a class of bis-phenyl compounds stated to mimic 1α, 25-dihydroxyvitamin D_3 is described in US Patent No. 6,218,430 and the article; "Novel nonsecosteroidal vitamin D mimics exert VDR-modulating activities with less calcium mobilization than 1α, 25-Dihydroxyvitamin D_3" by Marcus F. Boehm, et. al., Chemistry & Biology 1999, Vol 6, No. 5, pgs. 265-275.

Synthetic VDR ligands having an aryl-thiophene nucleus are described in United States provisional patent application SN 60/384151, filed 29 May 2002.

There remains a need for improved treatments using alternative or improved pharmaceutical agents that mimic $1\alpha,25(OH)_2D_3$ to stimulate bone formation, restore bone quality, and treat other diseases without the attendant disadvantage of hypercalcemia.

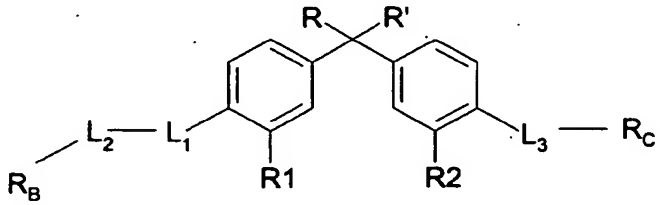
SUMMARY OF THE INVENTION

Novel compounds having a nucleus of formula "(AA)" have been found effective as Vitamin D Receptor (VDR) modulators:



(AA)

The compounds of the invention with VDR modulating activities are represented by formula (I)



(I)

wherein the variables R, R', R1, R2, L_1, L_2, L_3, and R_C are as hereinafter defined. It is a discovery of this invention that compounds described herein display the desirable cell differentiation and antiproliferative effects of $1,25(OH)_2D_3$ with reduced calcium mobilization (calcemic) effects if substituent R_C possesses a sulfonate or sulfonamide substituent.

In another aspect, the present invention is directed towards pharmaceutical compositions containing pharmaceutically effective amounts of compound of the invention or a pharmaceutically acceptable salt or prodrug thereof, either singly or in combination, together with pharmaceutically acceptable carriers and/or auxiliary agents.

Another aspect of the invention is a pharmaceutical formulation for treatment or prevention of osteoporosis containing pharmaceutically effective amounts of the vitamin D receptor modulator compound of the invention together with pharmaceutically effective amounts of co-agents conventionally used for the treatment of osteoporosis.

Another aspect of the invention is a pharmaceutical formulation for treatment or prevention of psoriasis containing pharmaceutically effective amounts of the vitamin D receptor modulator compound of the invention together with pharmaceutically effective

amounts of co-agents conventionally used for the treatment of psoriasis.

Another aspect of the invention is to use the compounds of the invention to treat disease states responsive to Vitamin D receptor ligands.

Another aspect of the invention is the prevention and treatment of acne, actinic keratosis, alopecia, Alzheimer's disease, autoimmune induced diabetes, bone fracture healing, breast cancer, Crohn's disease, prostate cancer, colon cancer, Type I diabetes, host-graft rejection, hypercalcemia , Type II diabetes, leukemia, multiple sclerosis, insufficient sebum secretion, osteomalacia, osteoporosis, insufficient dermal firmness, insufficient dermal hydration, myelodysplastic syndrome, psoriatic arthritis, psoriasis, renal osteodystrophy, rheumatoid arthritis, scleroderma, seborrheic dermatitis, skin cancer, systemic lupus erythematosis, skin cell damage from Mustard vesicants, ulcerative colitis and wrinkles; by administering to a mammal in need thereof a pharmaceutically effective amount of a compound of
the invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

The term, "abscess" refers to adverse complications often associated with surgery, trama, or diseases that predispose the host to abscess formation from encapsulated bacteria lymphocytes, macrophages, and etc.

The term, "adhesion" refers to the adverse and abnormal union of surfaces normally separate by the formation of new fibrous tissue resulting from an inflammatory process.

The term, "compound(s) of the invention" refers to one (or a plurality) of compounds described by Formulae I, II, or III or included in Tables 1, 2, or 3 or described in structural formulae A thru R or any of the compounds prepared as products in the Schemes or Examples set out herein.

The term, "Active Ingredient" means a compound of the invention.

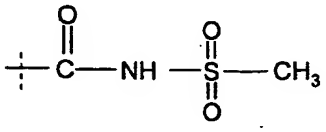
The term, "Mustard" is inclusive of both sulfur mustards and nitrogen mustards, either alone or in any combnation. Examplary of such compounds are the vesicants; bis(2-chloroethyl) sulfide (Chemical Agent Symbol HD), $Cl(CH_2)_2S(CH_2)_2Cl$ 1,2-bis(2-chloroethylthio)ethane (Chemical Agent Symbol Q), $Cl(CH_2)_2S(CH_2)_2S(CH_2)_2Cl$;

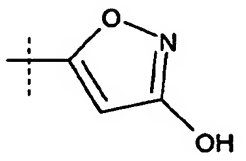
bis(2-chloroethylthioethyl) ether, $Cl(CH_2)_2S(CH_2)O(CH_2)_2S(CH_2)_2Cl$ (Chemical Agent Symbol T); tris(2-chloroethyl) amine (Chemical Agent Symbol HN3) $N(CH_2CH_2Cl)_3$; N-methyl-2,2'-dichlorodiethylamine (Chemical Agent Symbol NH2); and 2,2'-dichlorotriethylamine, $CH_3CH_2N(CH_2CH_2Cl)_2$ (Chemical Agent Symbol NH1).

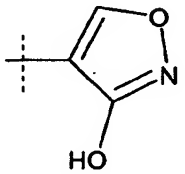
The term, "(Acidic Group)" means an organic group that acts as a proton donor capable of hydrogen bonding. Illustrative of an (Acidic Group) is a group selected from the following:

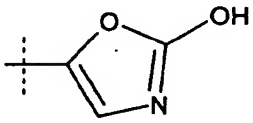
-C(O)OH,

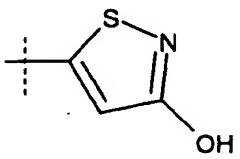
-5-tetrazolyl,

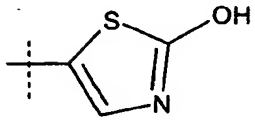


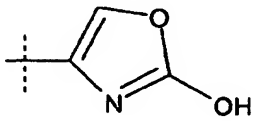


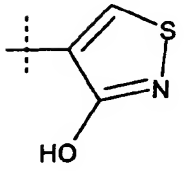


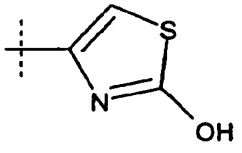


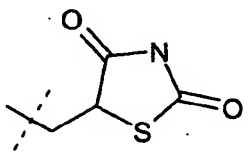








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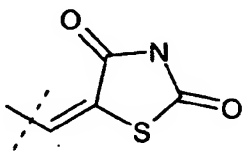
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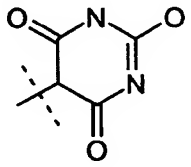
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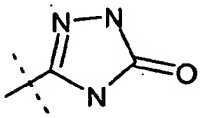
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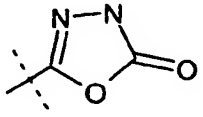
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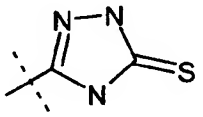
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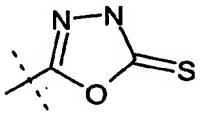
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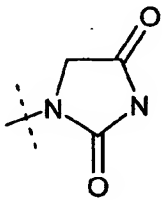
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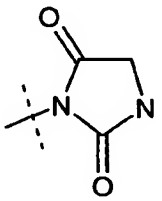
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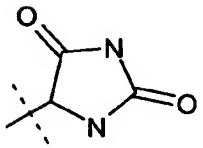
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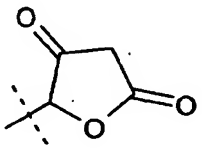
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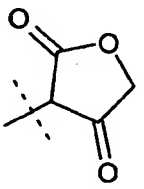
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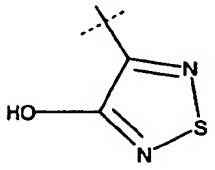
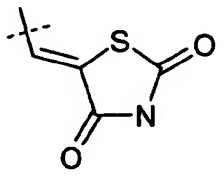
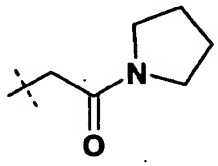
or



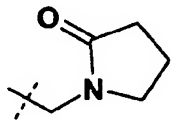
The term, "-1,3-thiazolidine-2,4-dione-5-ethtylidene", refers to the radical represented by the structural formula:



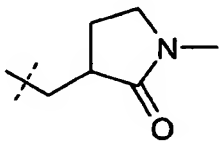
The term, "-CH_2-C(O)-N-pyrrolidine" refers to the radical represented by the structural formula:



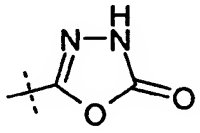
The term, "-CH_2-N-pyrrolidin-2-one" refers to the radical represented by the structural formula:



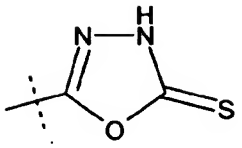
The term, "-CH_2-(1-methylpyrrolidin-2-one-3-yl)" refers to the organic radical represented by the structural formula:



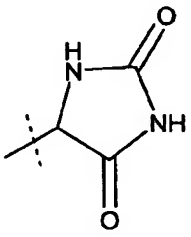
The term, "1,3,4-oxadiazolin-2-one-5-yl" refers to the organic radical represented by the structural formula:



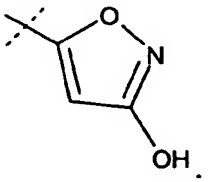
The term, "1,3,4-oxadiazolin-2-thione-5-yl" refers to the organic radical represented by the structural formula:



The terml, "imidazolidine-2,4-dione-5-yl" refers to the organic radical represented by the structural formula:

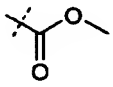


The term, "isoxazol-3-ol-5-yl" refers to the organic radical represented by the structural formula:



The dotted line symbol crossing a solid line representing a bond

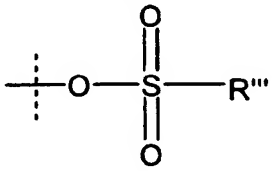
means that the bond so marked is the bond of attachement, for example, the group;



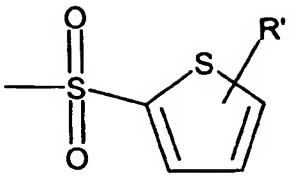
The term, "mammal" includes humans.

The term "halo" refer to fluorine, chlorine, bromine, and iodine.

The term "sulfonate" refers to the group

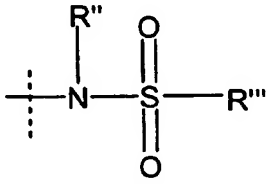


where R''' is C_1-C_5 alkyl, C_1-C_5 fluoroalkyl ,

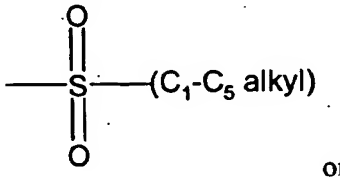


where R' is $-CO_2H$, $-CO_2R'''$, -OH, $-CF_3$, or C_1-C_5 alkyl.

The term "sulfonamide" refers to the group methyl, ethyl, branched C_3-C_5 alkyl,

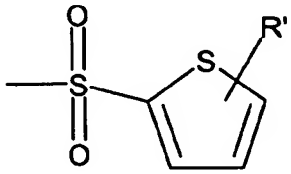


where R'' is H, C_1-C_5 alkyl, C_1-C_5 fluoroalkyl , or



or

where R''' is C_1-C_5 alkyl, C_1-C_5 fluoroalkyl ,



and

where R' is $-CO_2H$, $-CO_2R'''$, -OH, $-CF_3$, or C_1-C_5 alkyl.

The term, "C_{1-3} alkyl" refers to an alkyl group selected from methyl, ethyl, n-propyl, and isopropyl.

The term, "branched C_3-C_5 alkyl" is an alkyl group selected from 1-methylethyl; 1-methylpropyl; 2-methylpropyl; 1,1-dimethylethyl; 1,1-dimethylpropyl; 1,2-dimethylpropyl; or 2,2-dimethylpropyl. Preferred branched C_3-C_5 alkyl groups are 2-methylpropyl and 1,1-dimethylethyl, with the 1,1-dimethylethyl group being most preferred.

The term "alkenyl" refers to aliphatic groups wherein the point of attachment is a carbon-carbon double bond, for example vinyl, 1-propenyl, and 1-cyclohexenyl. Alkenyl

groups may be straight-chain, branched-chain, cyclic, or combinations thereof, and may be optionally substituted. Suitable alkenyl groups have from 2 to about 20 carbon atoms.

The term "C_1-C_5 alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain, and cyclic groups and any combinations thereof Examples of C_1-C_5 alkyl groups are methyl, ethyl, n-propyl, from 1-methylethyl; n-butyl, 1-methylpropyl; 2-methylpropyl; 1,1-dimethylethyl; n-amyl, 1,1-dimethylpropyl; 1,2-dimethylpropyl; and 2,2-dimethylpropyl.

The term "cycloalkyl" includes organic radicals such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term, "cycloalkenyl" includes organic radicals such as cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl.

The term, "C_1-C_5 fluoroalkyl"is an alkyl group containing fluorine and includes organic radicals such as -CF_3, -CHF_2, -CH_2F, -CF_2CF_3, -$CHFCF_3$, -CH_2CF_3, -CH_2CHF_2, and -CH_2CH_2F, with –CF_3 being preferred.

The abbreviation, "Me" means methyl.

The abbreviation, "Et" means ethyl.

The abbreviation, "iPr" means 1-methylethyl.

The abbreviation, "tBu" means 1,1-dimethylethyl.

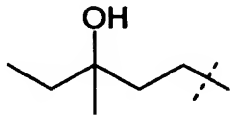
The term,"terminal hydroxyalkyl" is a group selected from

3-methyl-3-hydroxypentyl,
3-methyl-3-hydroxypentenyl,
3-methyl-3-hydroxypentynyl,
3-ethyl-3-hydroxypentyl,
3-ethyl-3-hydroxypentenyl,
3-ethyl-3-hydroxypentynyl,
3-ethyl-3-hydroxy-4-methylpentyl,
3-ethyl-3-hydroxy-4-methylpentenyl,
3-ethyl-3-hydroxy-4-methylpentynyl,
3-propyl-3-hydroxypentyl,
3-propyl-3-hydroxypentenyl,
3-propyl-3-hydroxypentynyl,
1-hydroxy-2-methyl-1-(methylethyl)propyl,

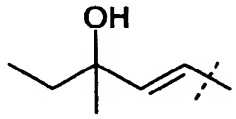
1-hydroxycycloalkenyl; or

1-hydroxycycloalkyl.

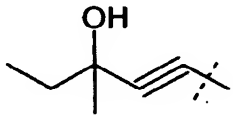
The term, "3-methyl-3-hydroxypentyl" refers to the radical having the structural formula:



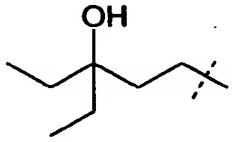
The term, "3-methyl-3-hydroxypentenyl" refers to the radical having the structural formula (both cis and trans isomers):



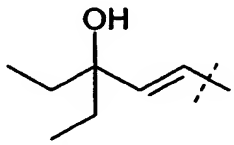
The term, "3-methyl-3-hydroxypentynyl" refers to the radical having the structural formula:



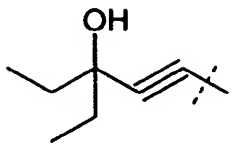
The term, "3-ethyl-3-hydroxypentyl" refers to the radical having the structural formula:



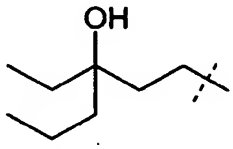
The term, "3-ethyl-3-hydroxypentenyl" refers to the radical having the structural formula (both cis and trans isomers):



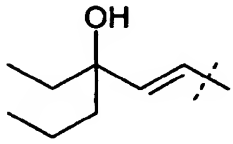
The term, "3-ethyl-3-hydroxypentynyl" refers to the radical having the structural formula:



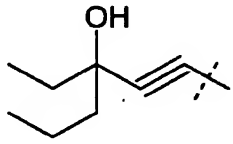
The term, "3-propyl-3-hydroxypentyl" refers to the radical having the structural formula:



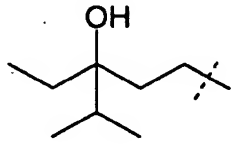
The term, "3-propyl-3-hydroxypentenyl" refers to the radical having the structural formula (both cis and trans isomers):



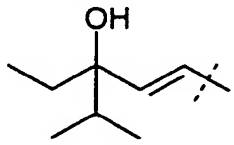
The term, "3-propyl-3-hydroxypentynyl" refers to the radical having the structural formula:



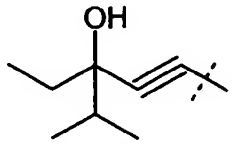
The term, "3-ethyl-3-hydroxy-4-methylpentyl" refers to the radical having the structural formula:



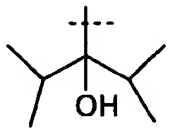
The term, "3-ethyl-3-hydroxy-4-methylpentenyl" refers to the radical having the structural formula (both cis and trans isomers):



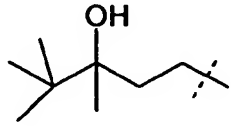
The term, "3-ethyl-3-hydroxy-4-methylpentynyl" refers to the radical having the structural formula:



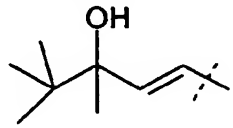
The term, "1-hydroxy-2-methyl-1-(methylethyl)propyl" refers to the radical having the structural formula:



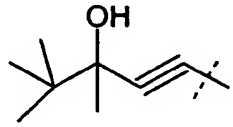
The term, "3-methyl-3-hydroxy-4,4-dimethylpentyl" refers to the radical having the structural formula:



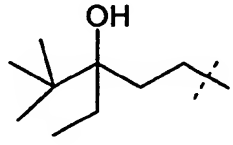
The term, "3-methyl-3-hydroxy-4,4-dimethylpentenyl." refers to the radical having the structural formula (both cis and trans isomers):



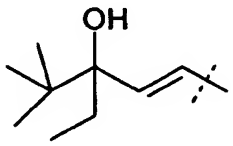
The term, "3-methyl-3-hydroxy-4,4-dimethylpentyl" refers to the radical having the structural formula:



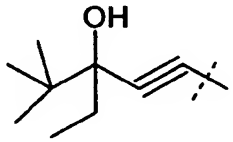
The term, "3-ethyl-3-hydroxy-4,4-dimethylpentynyl" refers to the radical having the structural formula:



The term, "3-ethyl-3-hydroxy-4,4-dimethylpentenyl" refers to the radical having the structural formula (both cis and trans isomers):

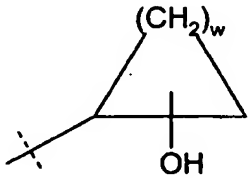


The term, "3-ethyl-3-hydroxy-4,4-dimethylpentynyl" refers to the radical having the structural formula:



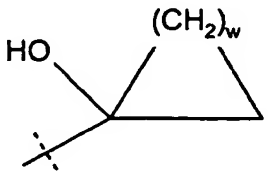
The term, "1-hydroxycycloalkenyl" refers to a radical selected from 1-hydroxycyclopentenyl, 1-hydroxycyclohexenyl, 1-hydroxycycloheptenyl, or 1-hydroxycyclooctenyl.

The term "hydroxycycloalkyl" refers to a radical having the general structural formula:



where w is an integer from 1 to 6 and the hydroxyl radical is substituted on any ring carbon atom.

The term "1-hydroxycycloalkyl" refers to a radical having the general structural formula:



Examples of 1-hydroxycycloalkyl radicals are 1-hydroxycyclopropyl, 1-hydroxycyclobutyl, 1-hydroxycyclopentyl, 1-hydroxycyclohexyl, 1-hydroxycycloheptyl, and 1-hydroxycyclooctyl.

The abbreviation, "Me" means methyl.

The abbreviation, "Et" means ethyl.

The abbreviation, "iPr" means 1-methylethyl.

The abbreviation, "nPr" means n-propyl.

The abbreviation, "3Me3OH-Pentyl" means 3-methyl-3-hydroxypentyl.

The abbreviation, "3Me3OH-Pentenyl" means 3-methyl-3-hydroxypentenyl

The abbreviation, "3Me3OH-Pentynyl" means 3-methyl-3-hydroxypentynyl

The abbreviation, "3Et3OH-Pentyl" means 3-ethyl-3-hydroxypentyl.

The abbreviation, "3Et3OH-Pentenyl" means 3-ethyl-3-hydroxypentenyl

The abbreviation, "3Et3OH-Pentynyl" means 3-ethyl-3-hydroxypentynyl

The abbreviation, "3Pr3OH-Pentyl" means 3-propyl-3-hydroxypentyl.

The abbreviation, "3Pr3OH-Pentenyl" means 3-propyl-3-hydroxypentenyl.

The abbreviation, "3Pr3OH-Pentynyl" means 3-propyl-3-hydroxypentynyl.

The abbreviation, "3Et3OH4Me-Pentyl" means 3-ethyl-3-hydroxy-4-methylpentyl.

The abbreviation, "3Et3OH4Me-Pentenyl" means 3-ethyl-3-hydroxy-4-methylpentenyl,

The abbreviation, "3Et3OH4Me-Pentynyl" means 3-ethyl-3-hydroxy-4-methylpentynyl.

The abbreviation, "1OH2Me1MeEt-Propyl" means 1-hydroxy-2-methyl-1-(methylethyl)propyl.

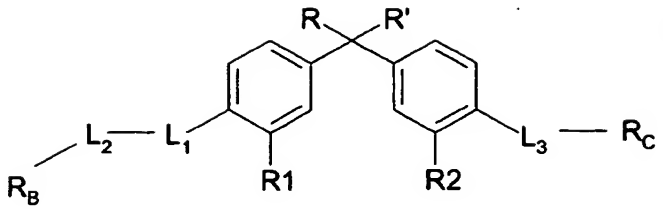
The dotted line symbol crossing a solid line representing a bond

means that the bond so marked is the bond of attachment.

The term, "mammal" includes humans.

Compounds of the Invention:

The compounds of the invention with vitamin receptor modulating (VDRM) activity are represented by formula (I) or a pharmaceutically acceptable salt or a prodrug derivative thereof:



(I)

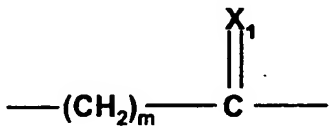
wherein;

R and R' are independently C_1-C_5 alkyl, C_1-C_5 fluoroalkyl, or together R and R' form a substituted or unsubstituted, saturated or unsaturated carbocyclic ring having from 3 to 8 carbon atoms;

R1 and R2 are independently selected from the group consisting of hydrogen, halo, C_1-C_5 alkyl, C_1-C_5 fluoroalkyl, -O-C_1-C_5 alkyl, -S-C_1-C_5 alkyl, -O-C_1-C_5 fluoroalkyl, -CN, -NO_2, acetyl, -S-C_1-C_5 fluoroalkyl, C_2-C_5 alkenyl, C_3-C_5 cycloalkyl, and C_3-C_5 cycloalkenyl;

L_1 and L_2 and L_3 are independently divalent linking groups independently selected from the group consisting of

a bond ,



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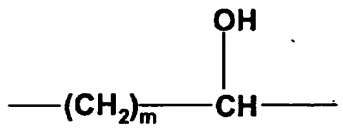

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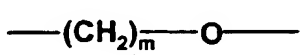

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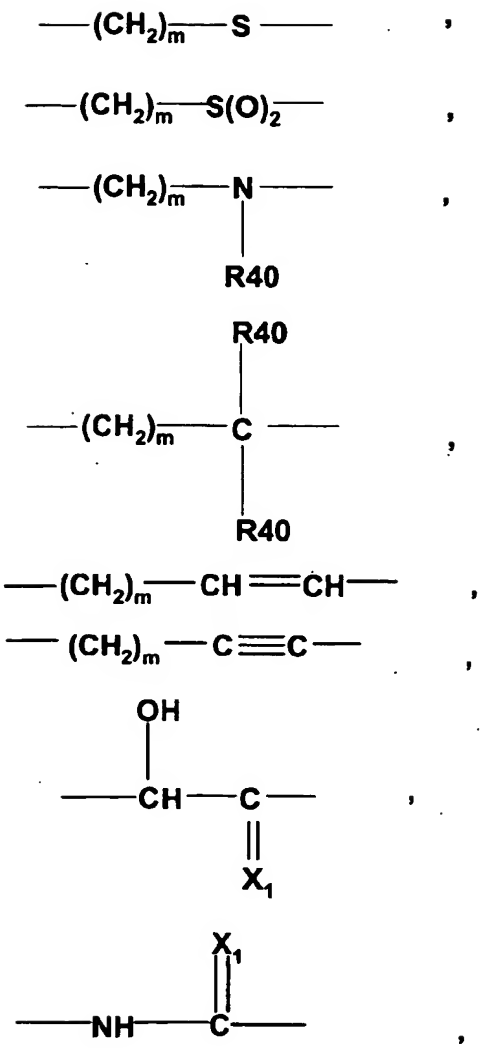


where m is 0, 1 or 2, X_1 is oxygen or sulfur, and each R40 is independently hydrogen, C_1-C_5 alkyl, or C_1-C_5 fluoroalkyl;

R_B is

branched C_3-C_5 alkyl,

3-methyl-3-hydroxypentyl,

3-methyl-3-hydroxypentenyl,

3-methyl-3-hydroxypentynyl,

3-ethyl-3-hydroxypentyl,

3-ethyl-3-hydroxypentenyl,

3-ethyl-3-hydroxypentynyl,

3-ethyl-3-hydroxy-4-methylpentyl,

3-ethyl-3-hydroxy-4-methylpentenyl,
3-ethyl-3-hydroxy-4-methylpentynyl,
3-propyl-3-hydroxypentyl,
3-propyl-3-hydroxypentenyl,
3-propyl-3-hydroxypentynyl,
1-hydroxy-2-methyl-1-(methylethyl)propyl,
3-methyl-3-hydroxy-4,4-dimethylpentyl,
3-methyl-3-hydroxy-4,4-dimethylpentenyl,
3-methyl-3-hydroxy-4,4-dimethylpentyl,
3-ethyl-3-hydroxy-4,4-dimethylpentynyl,
3-ethyl-3-hydroxy-4,4-dimethylpentenyl,
3-ethyl-3-hydroxy-4,4-dimethylpentynyl,
4,4-dimethyl-3-hydroxypropyl,
1-hydroxycyclopentenyl,
1-hydroxycyclohexenyl,
1-hydroxycycloheptenyl,
1-hydroxycyclooctenyl,
1-hydroxycyclopropyl,
1-hydroxycyclobutyl,
1-hydroxycyclopentyl,
1-hydroxycyclohexyl,
1-hydroxycycloheptyl, or
1-hydroxycyclooctyl;

provided, however, that when

R_B is

3-methyl-3-hydroxypentyl,
3-methyl-3-hydroxypentenyl,
3-methyl-3-hydroxypentynyl,
3-ethyl-3-hydroxypentyl,
3-ethyl-3-hydroxypentenyl,
3-ethyl-3-hydroxypentynyl,
4,4-dimethyl-3-hydroxypropyl,

3-ethyl-3-hydroxy-4-methylpentyl,
3-ethyl-3-hydroxy-4-methylpentenyl,
3-ethyl-3-hydroxy-4-methylpentynyl,
3-propyl-3-hydroxypentyl,
3-propyl-3-hydroxypentenyl,
3-propyl-3-hydroxypentynyl,
3-methyl-3-hydroxy-4,4-dimethylpentyl,
3-methyl-3-hydroxy-4,4-dimethylpentenyl,
3-methyl-3-hydroxy-4,4-dimethylpentyl,
3-ethyl-3-hydroxy-4,4-dimethylpentynyl,
3-ethyl-3-hydroxy-4,4-dimethylpentenyl,
3-ethyl-3-hydroxy-4,4-dimethylpentynyl, or
1-hydroxy-2-methyl-1-(methylethyl)propyl;

then L_1 and L_2 combine as a bond; and

R_C is

-O-SO_2-(R50)

where R50 is

-C_{1-3}alkyl, -CF_3, -$(CH_2)_{1-2}CF_3$,
-S-C_{1-3}alkyl , -SO_2-C_{1-3}alkyl,
-$(CH_2)_{1-2}$C(O)NHMe,
-$(CH_2)_{1-2}$-CO_2H; or

-NH-SO_2-(R50)

where R50 is

-C_{1-3}alkyl, -CF_3, -$(CH_2)_{1-2}CF_3$,
-S-C_{1-3}alkyl , -SO_2-C_{1-3}alkyl,
-$(CH_2)_{1-2}$-CO_2H,
-$(CH_2)_{1-2}$C(O)NHMe, or

$-N(SO_2R51)_2$

where each R51 is independently,

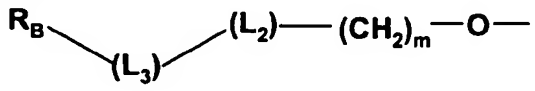
$-C_{1-3}$alkyl, $-CF_3$, $-(CH_2)_{1-2}CF_3$,

$-(CH_2)_{1-2}C(O)NHMe$,

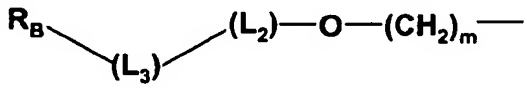
$-S-C_{1-3}$alkyl , $-SO_2-C_{1-3}$alkyl, or

$-(CH_2)_{1-2}-CO_2H$.

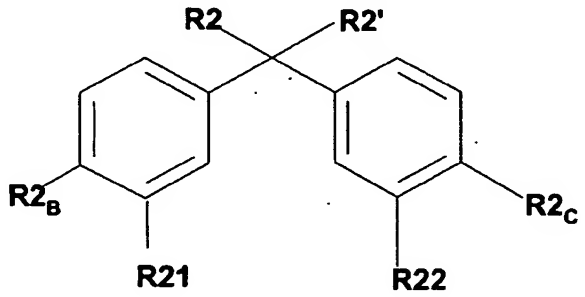
In the preceding formula I the divalent linking groups to be oriented in either direction, for example, where divalent linker (L_1) has the identity $-(CH_2)_m-O-$, it may be configured:



or



Preferred compounds of the invention with VDR modulating activities are represented by formula (II) or a pharmaceutically acceptable salt or a prodrug derivative thereof:



(II)

wherein;

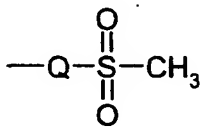
R2 and R2' are independently methyl or ethyl;

R21 and R22 are independently selected from the group consisting of hydrogen, fluoro, -Cl, $-CF_3$, $-CH_2F$, $-CHF_2$, methoxy, ethoxy, vinyl, methyl, ethyl, propyl, 1-methylethyl, 1,1-dimethylethyl, butyl, 1-methylpropyl, 2-methylpropyl, or cyclopropyl;

$R2_B$ is a group represented by the formula:

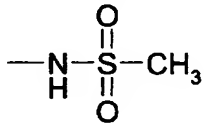
3-methyl-3-hydroxypentyl,
3-methyl-3-hydroxypentenyl,
3-methyl-3-hydroxypentynyl,
3-ethyl-3-hydroxypentyl,
3-ethyl-3-hydroxypentenyl,
3-ethyl-3-hydroxypentynyl,
3-ethyl-3-hydroxy-4-methylpentyl,
3-ethyl-3-hydroxy-4-methylpentenyl,
3-ethyl-3-hydroxy-4-methylpentynyl,
3-propyl-3-hydroxypentyl,
3-propyl-3-hydroxypentenyl,
3-propyl-3-hydroxypentynyl,
1-hydroxy-2-methyl-1-(methylethyl)propyl

$R2_C$ is



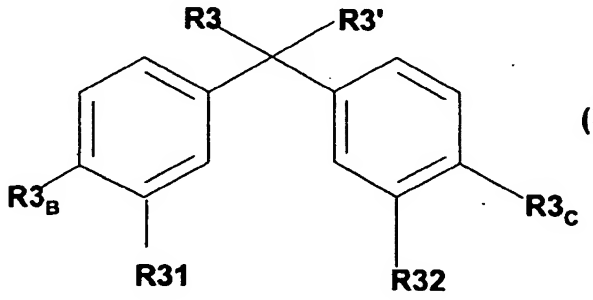
wherein Q is –O- or –NH-.

Preferred compounds have the substituent $R2_C$ of formula II as:



;

Preferred compounds of the invention with VDR modulating activities are represented by formula (III) or a pharmaceutically acceptable salt or a prodrug derivative thereof:



(III)

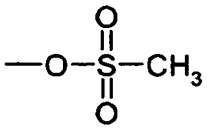
wherein;

R3 and R3' are independently methyl or ethyl;

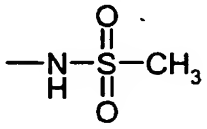
R31 and R32 are independently selected from the group consisting of hydrogen, fluoro, -Cl, -CF_3, -CH_2F, -CHF_2, methoxy, ethoxy, vinyl, methyl, ethyl, propyl, 1-methylethyl, 1,1-dimethylethyl, butyl, 1-methylpropyl, 2-methylpropyl, or cyclopropyl;

$R3_B$ is 3-hydroxy-3-ethyl-pentyl or 4,4-dimethyl(-3-hydroxypropyl).

$R3_C$ is

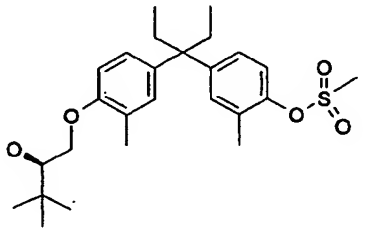


or

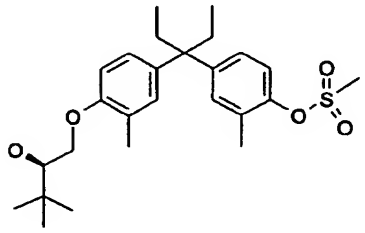


Preferred compounds of the invention are represented by the structural formulae M-1 to M-31 as follows:

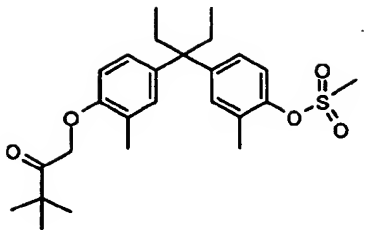
M-1)



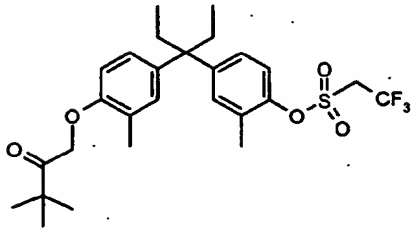
M-2)



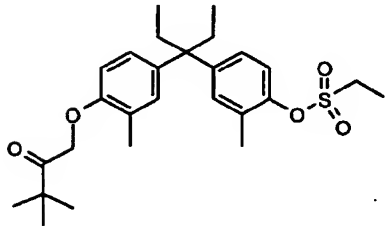
M-3)



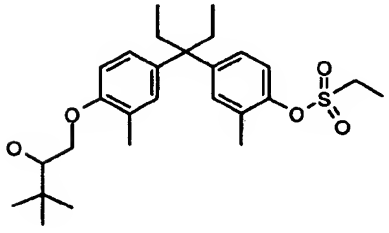
M-6)



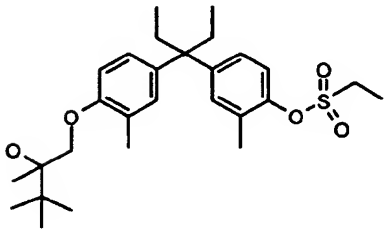
M-7)



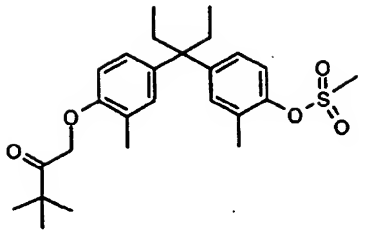
M-8)



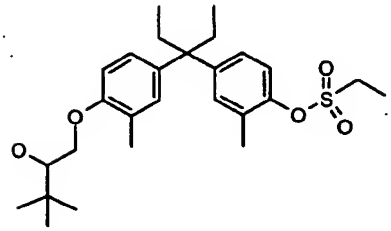
M-9)



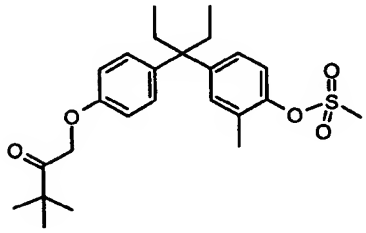
M-10)



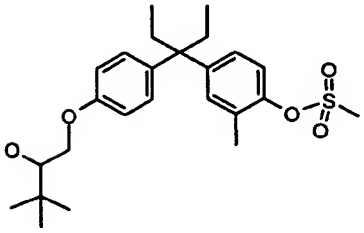
M-11)



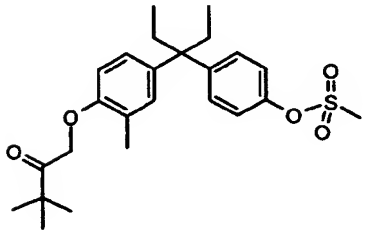
M-13)



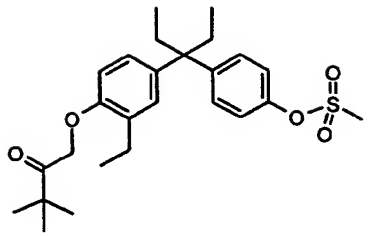
M-14)



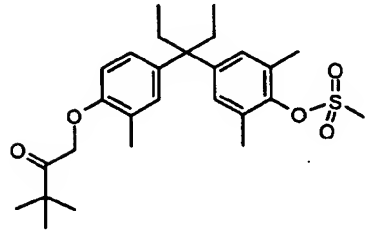
M-15)



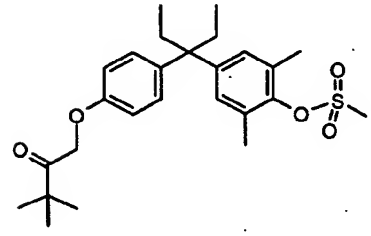
M-16)



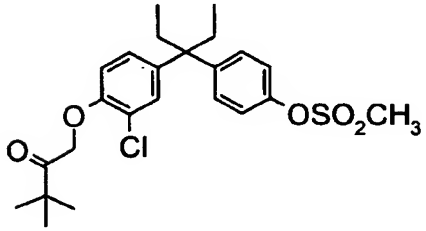
M-17)



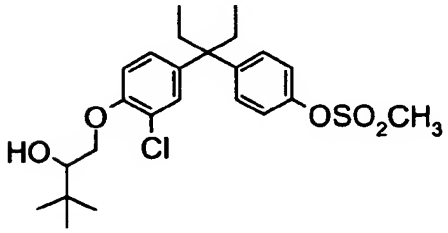
M-18)



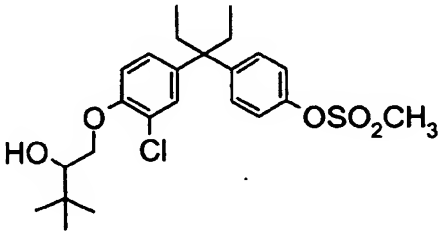
M-19)



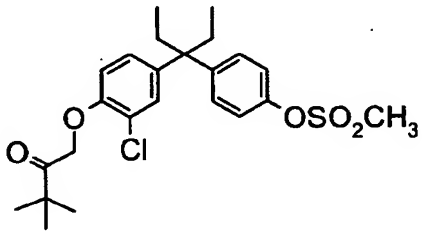
M-20)



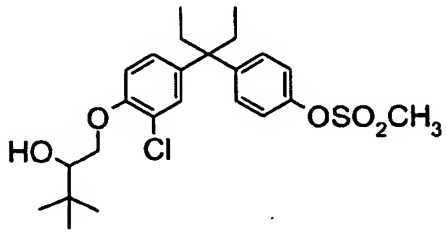
M21)



M-26)

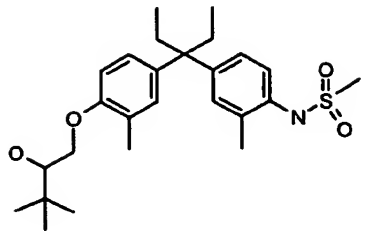


M-27)

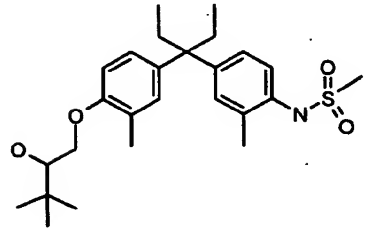


Preferred sulfonamide functional compounds of the invention are represented by the structural formulae M-32 to M-50 as follows:

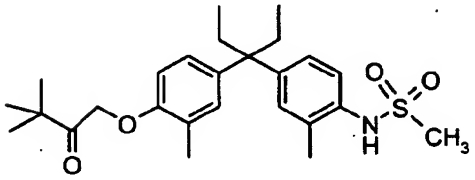
M-32)



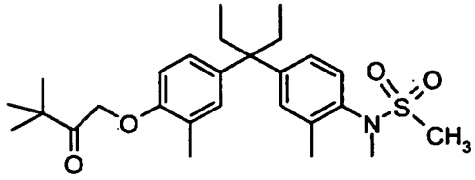
M-33)



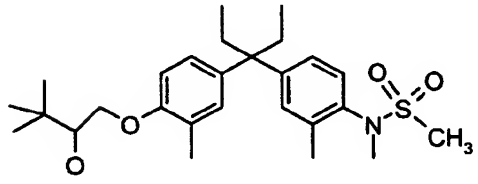
M-34)



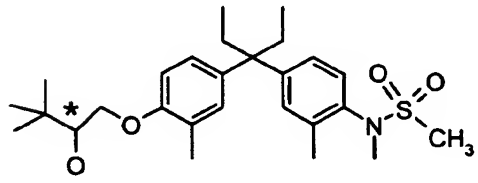
M-35)



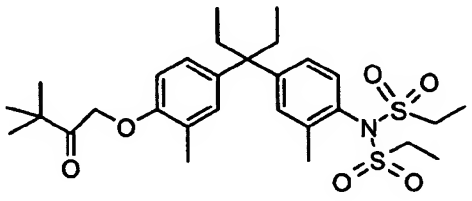
M-36)



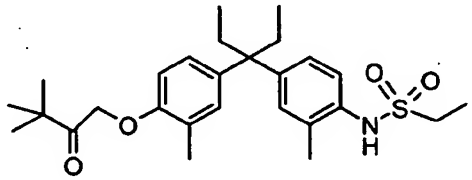
M-37)



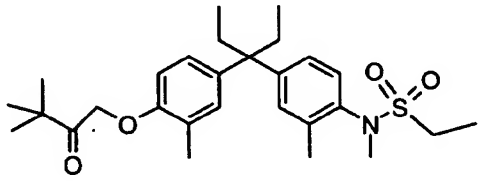
M-38)



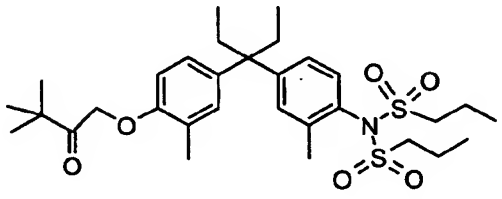
M-39)



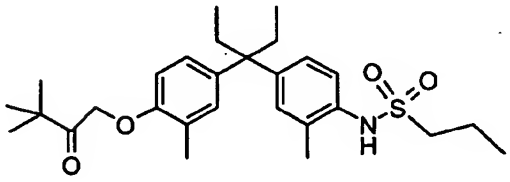
M-40)



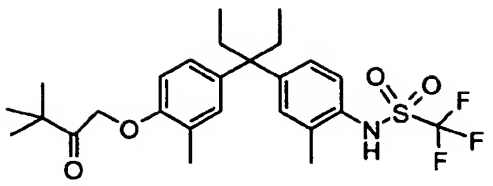
M-41)



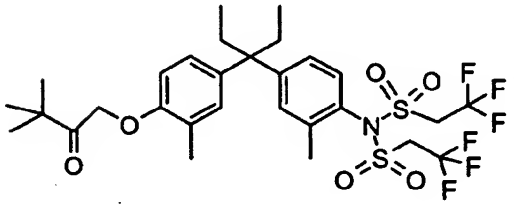
M-42)



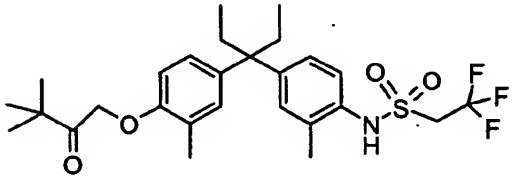
M-43)



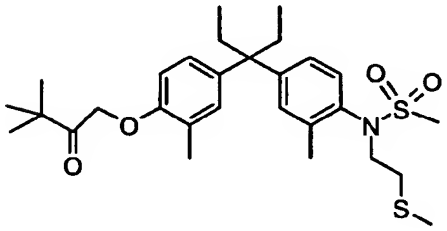
M-44)



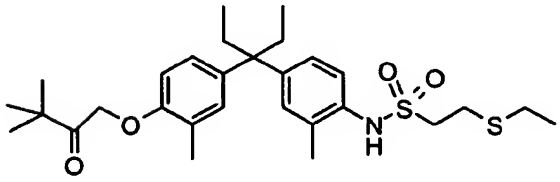
M-45)



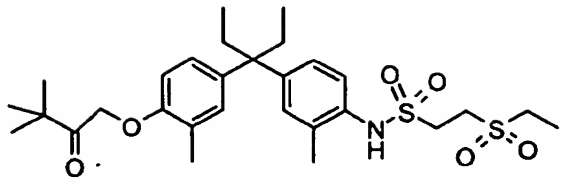
M-46)



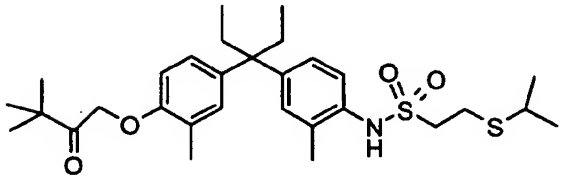
M-47)



M-48)

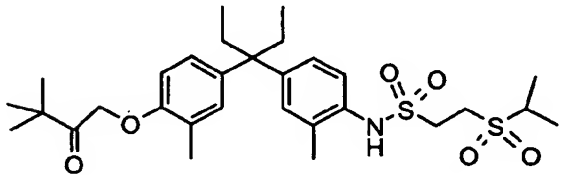


M-49)

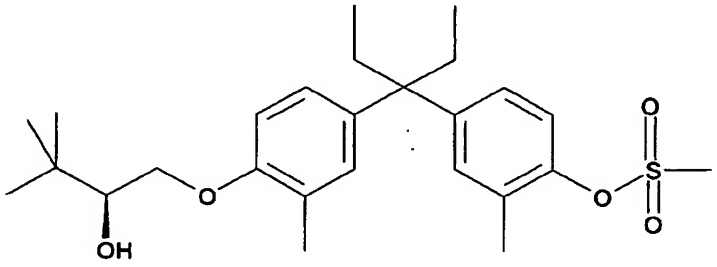


or

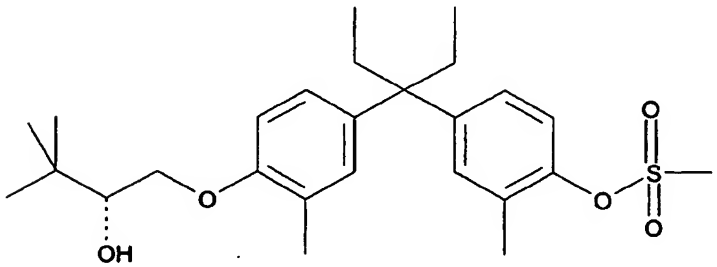
M-50)



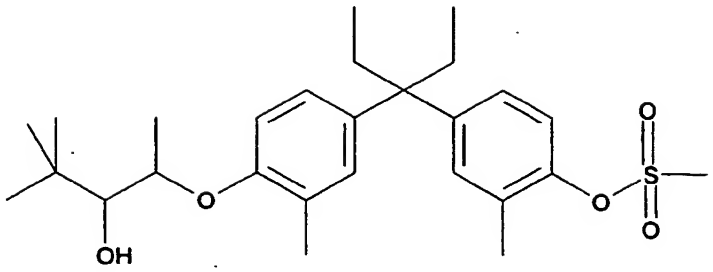
Other preferred compounds of the invention are represented by the formula:

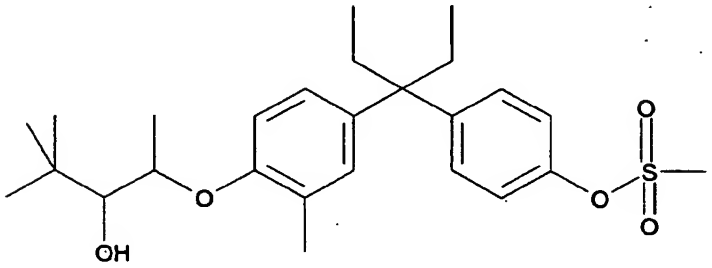


or

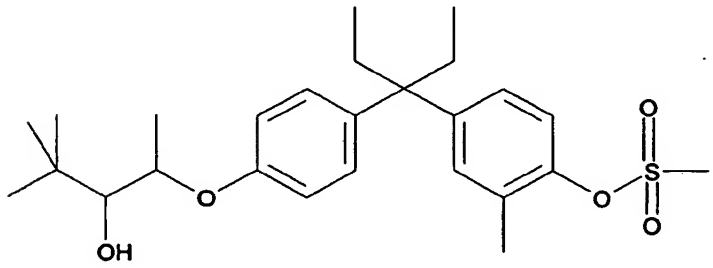


Other preferred compounds of the invention are represented by the formula:

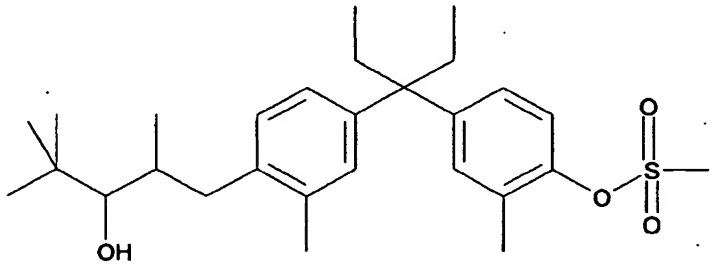




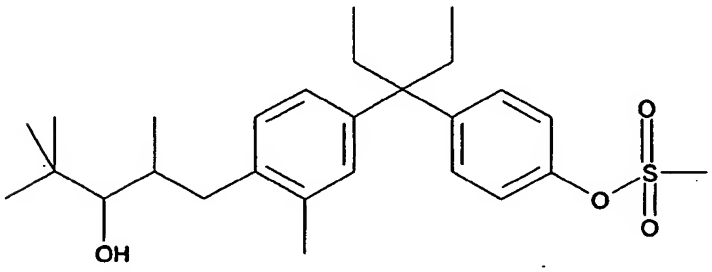
, or



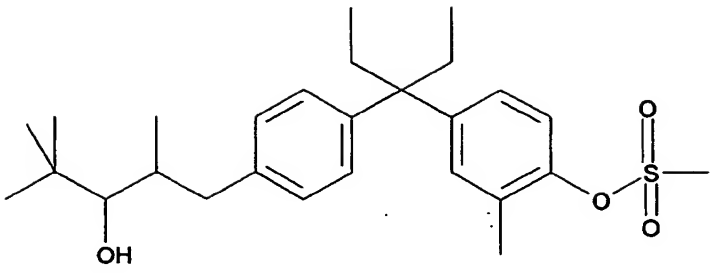
Other preferred compounds of the invention are represented by the formula:



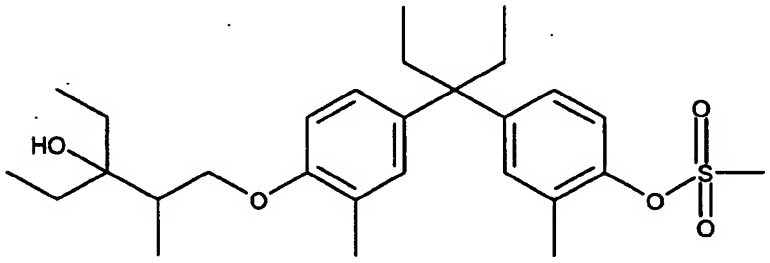
,



, or



Other preferred compounds of the invention are represented by the formula:



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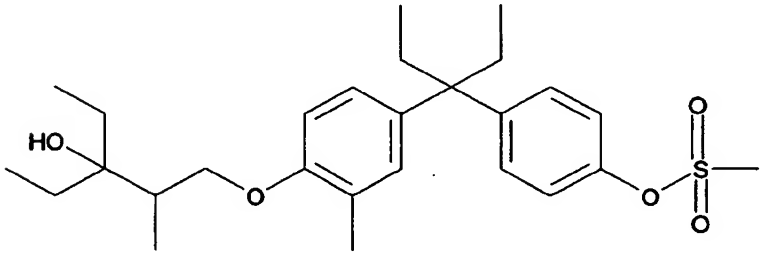

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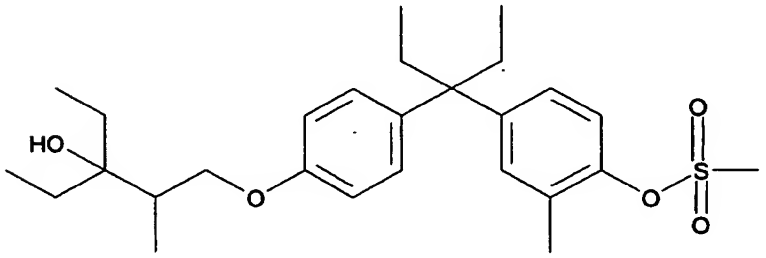

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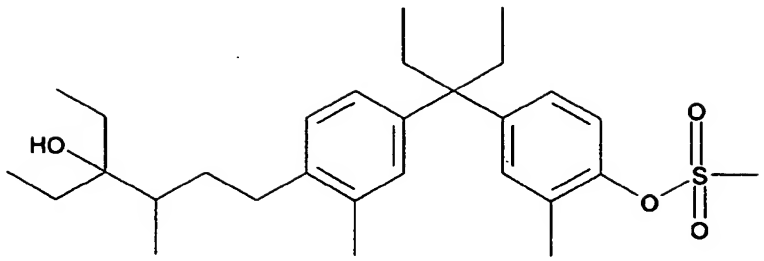
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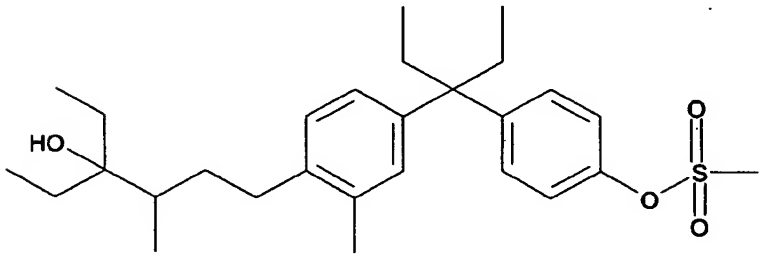
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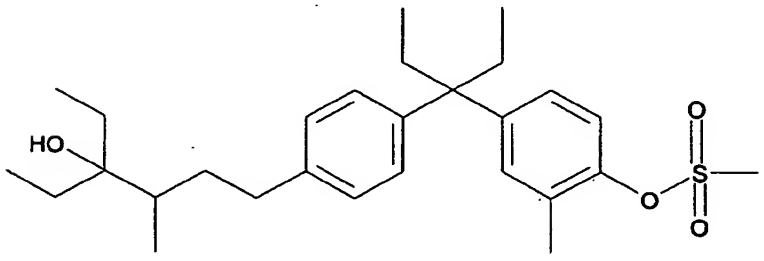
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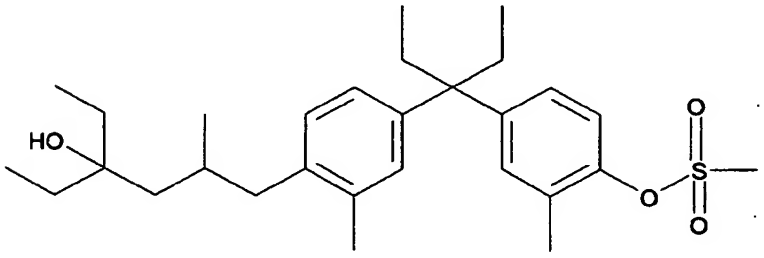
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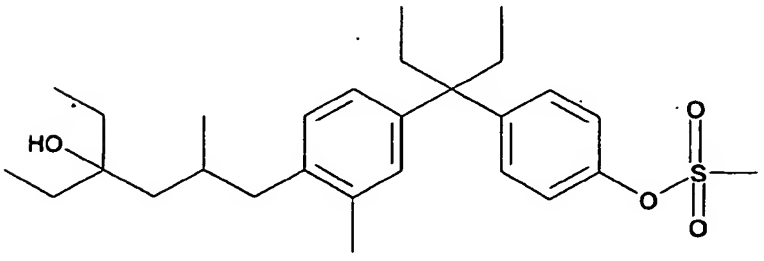
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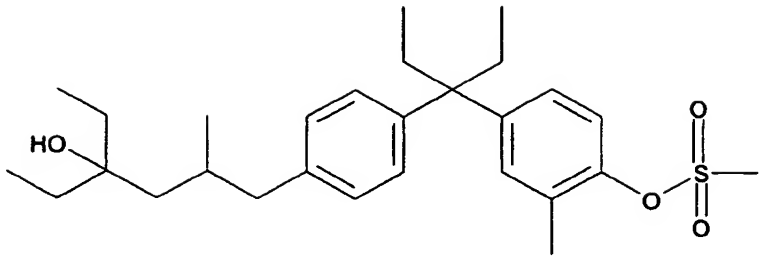

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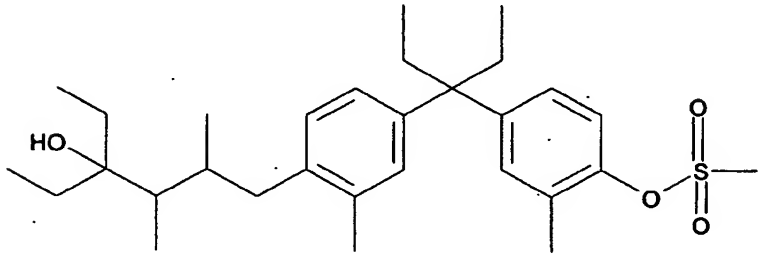

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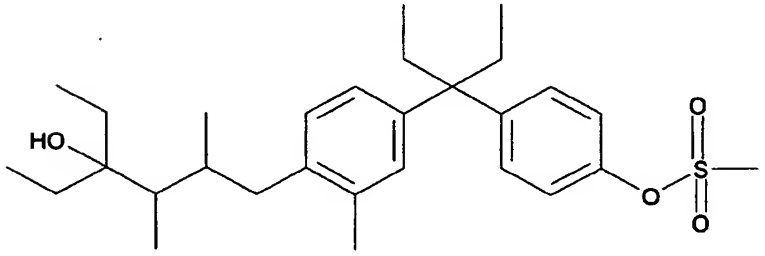

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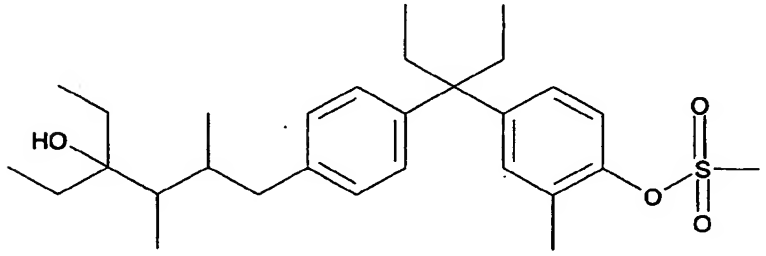
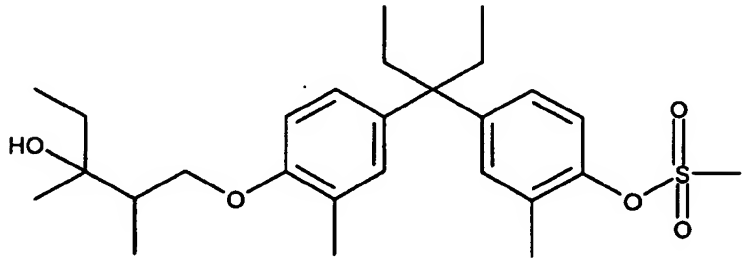


Other preferred compounds of the invention are represented by the formula:



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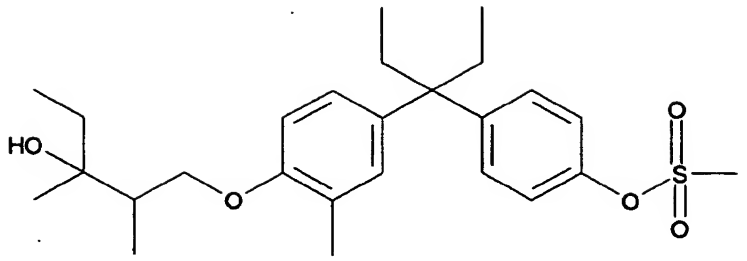
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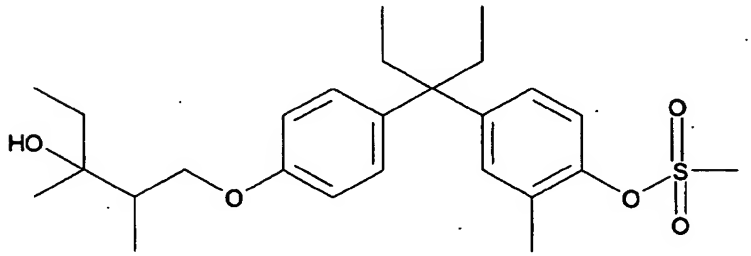
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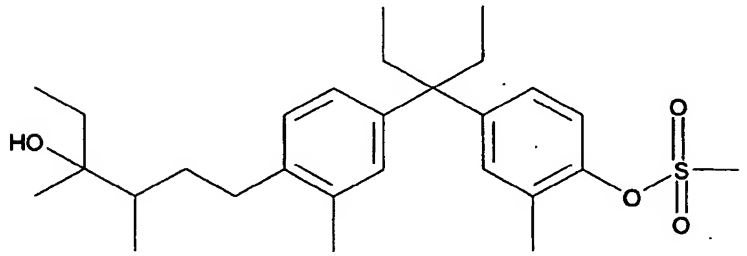
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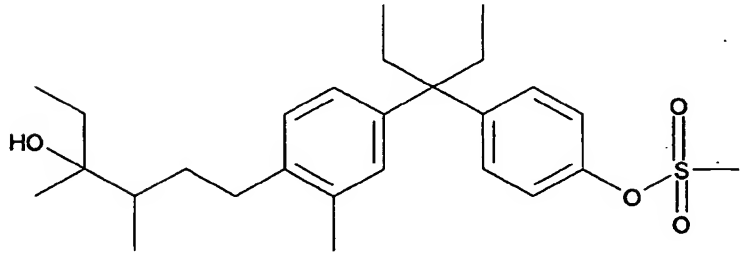
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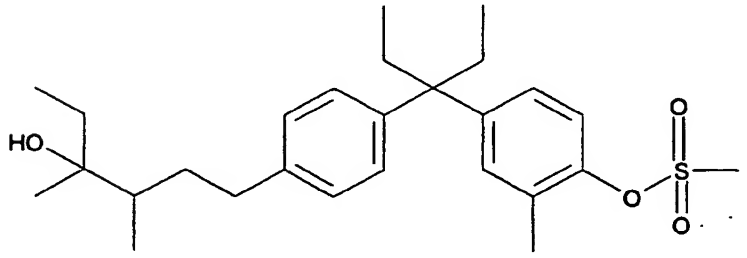
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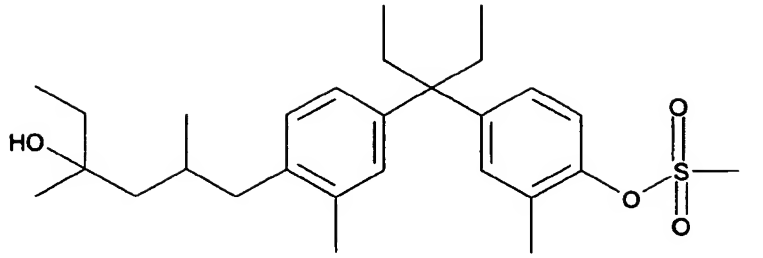

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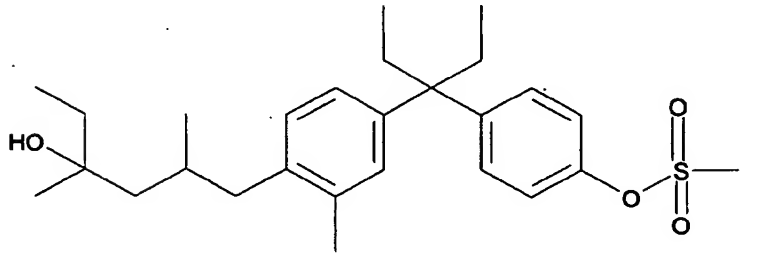

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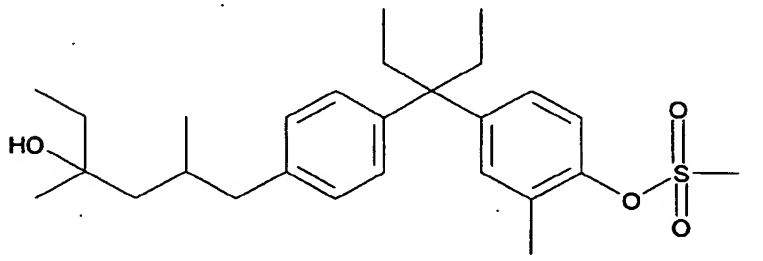

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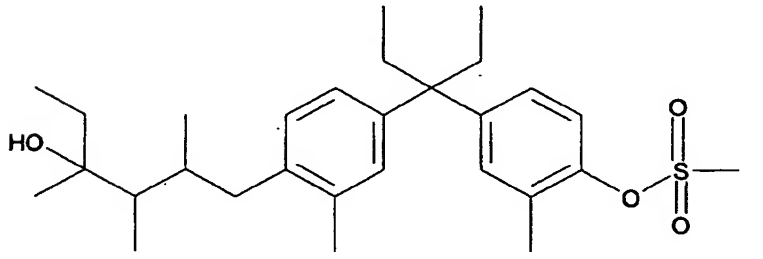

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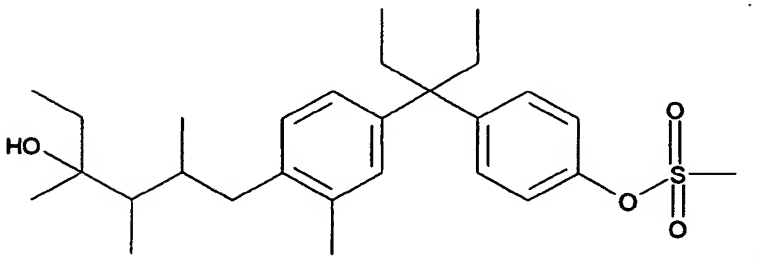

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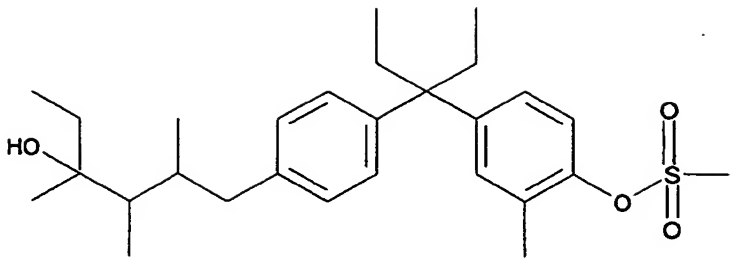
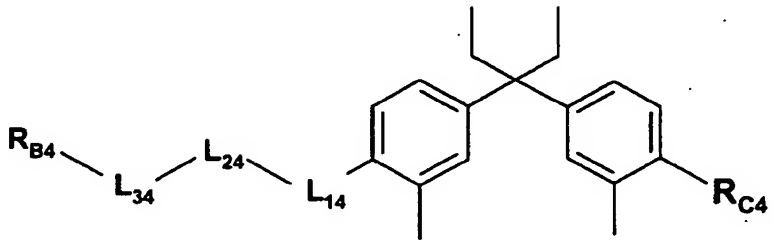


Other specific compounds and pharmaceutically acceptable salts and prodrug derivatives thereof, that are preferred embodiments of this invention and are preferred for for practicing the method of treatment of the invention are set out in the following three Tables. All numbers in the Tables cells reciting chemical species (except for the abbreviation "3Et3OH-Pentyl")are to be understood as subscripts in chemical formulae, for example, in row, Code 11, Column, R_{C4}, the symbol, "-O-S(O)2Me" is to be understood as the conventional chemical nomenclature, -O-S(O)$_2$Me. Each row of the Tables is a single compound having an identifying "Code" (e.g., "14", "33A, 21B") defining the specific substituents in the structural formula displayed above each Table, as follows:

A preferred compounds of the invention or a pharmaceutically acceptable salt or an ester prodrug derivative thereof represented by the formula:



where said compound is selected from a compound code numbered 1 thru 135, with each compound having the specific selection of substituents R_{B4}, R_{C4}, L_{14}, L_{24}, L_{34}, and RC4 shown in the row following the compound code number, as set out in the following Table 1 :

Table 1

Code	R_{B4}	L_{34}	L_{24}	L_{14}	R_{C4}

No.					
1	tBu	C(O)	CH2	O	-O-S(O)2Me
2	tBu	C(O)	CH2	CH2	-O-S(O)2Me
3	tBu	C(O)	CH(ME)	CH2	-O-S(O)2Me
4	tBu	CHOH	CH2	O	-O-S(O)2Me
5	tBu	CHOH	CH2	CH2	-O-S(O)2Me
6	tBu	CHOH	CH(ME)	CH2	-O-S(O)2Me
7	tBu	C(Me)OH	CH2	O	-O-S(O)2Me
8	tBu	C(Me)OH	CH2	CH2	-O-S(O)2Me
9	tBu	C(Me)OH	CH(ME)	CH2	-O-S(O)2Me
10	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Me
11	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Me
12	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Me
13	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Me
14	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Me
15	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Me
16	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Me
17	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Me
18	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Me
19	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Me
20	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2Me
21	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Me
22	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Me
23	1-hydroxycyclohexy	bond	CH2	CH2	-O-S(O)2Me
24	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Me
25	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Me
26	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2Me
27	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Me
28	tBu	C(O)	CH2	O	-O-S(O)2Et
29	tBu	C(O)	CH2	CH2	-O-S(O)2Et
30	tBu	C(O)	CH(ME)	CH2	-O-S(O)2Et

31	tBu	CHOH	CH2	O	-O-S(O)2Et
32	tBu	CHOH	CH2	CH2	-O-S(O)2Et
33	tBu	CHOH	CH(ME)	CH2	-O-S(O)2Et
34	tBu	C(Me)OH	CH2	O	-O-S(O)2Et
35	tBu	C(Me)OH	CH2	CH2	-O-S(O)2Et
36	tBu	C(Me)OH	CH(ME)	CH2	-O-S(O)2Et
37	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Et
38	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Et
39	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Et
40	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Et
41	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Et
42	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Et
43	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Et
44	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Et
45	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Et
46	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Et
47	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2Et
48	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Et
49	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Et
50	1-hydroxycyclohexy	bond	CH2	CH2	-O-S(O)2Et
51	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Et
52	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Et
53	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2Et
54	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Et
55	tBu	C(O)	CH2	O	-O-S(O)2CH2CO2H
56	tBu	C(O)	CH2	CH2	-O-S(O)2CH2CO2H
57	tBu	C(O)	CH(ME)	CH2	-O-S(O)2CH2CO2H
58	tBu	CHOH	CH2	O	-O-S(O)2CH2CO2H
59	tBu	CHOH	CH2	CH2	-O-S(O)2CH2CO2H
60	tBu	CHOH	CH(ME)	CH2	-O-S(O)2CH2CO2H
61	tBu	C(Me)OH	CH2	O	-O-S(O)2CH2CO2H

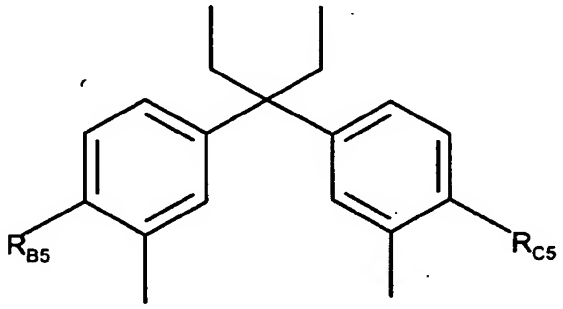
62	tBu	C(Me)OH	CH2	CH2	-O-S(O)2CH2CO2H
63	tBu	C(Me)OH	CH(ME)	CH2	-O-S(O)2CH2CO2H
64	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2CH2CO2H
65	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2CH2CO2H
66	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
67	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2CH2CO2H
68	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2CH2CO2H
69	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
70	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2CH2CO2H
71	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2CH2CO2H
72	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
73	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2CH2CO2H
74	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2CH2CO2H
75	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
76	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2CH2CO2H
77	1-hydroxycyclohexy	bond	CH2	CH2	-O-S(O)2CH2CO2H
78	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
79	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2CH2CO2H
80	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2CH2CO2H
81	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
82	tBu	C(O)	CH2	O	-NH-S(O)2Me
83	tBu	C(O)	CH2	CH2	-NH-S(O)2Me
84	tBu	C(O)	CH(ME)	CH2	-NH-S(O)2Me
85	tBu	CHOH	CH2	O	-NH-S(O)2Me
86	tBu	CHOH	CH2	CH2	-NH-S(O)2Me
87	tBu	CHOH	CH(ME)	CH2	-NH-S(O)2Me
88	tBu	C(Me)OH	CH2	O	-NH-S(O)2Me
89	tBu	C(Me)OH	CH2	CH2	-NH-S(O)2Me
90	tBu	C(Me)OH	CH(ME)	CH2	-NH-S(O)2Me
91	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2Me
92	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2Me

93	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2Me
94	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2Me
95	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2Me
96	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2Me
97	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2Me
98	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2Me
99	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2Me
100	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2Me
101	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2Me
102	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2Me
103	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2Me
104	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2Me
105	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2Me
106	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2Me
107	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2Me
108	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2Me
109	tBu	C(O)	CH2	O	-NH-S(O)2CH2CO2H
110	tBu	C(O)	CH2	CH2	-NH-S(O)2CH2CO2H
111	tBu	C(O)	CH(ME)	CH2	-NH-S(O)2CH2CO2H
112	tBu	CHOH	CH2	O	-NH-S(O)2CH2CO2H
113	tBu	CHOH	CH2	CH2	-NH-S(O)2CH2CO2H
114	tBu	CHOH	CH(ME)	CH2	-NH-S(O)2CH2CO2H
115	tBu	C(Me)OH	CH2	O	-NH-S(O)2CH2CO2H
116	tBu	C(Me)OH	CH2	CH2	-NH-

					S(O)2CH2CO2H
117	tBu	C(Me)OH	CH(ME)	CH2	-NH-S(O)2CH2CO2H
118	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2CH2CO2H
119	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
120	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H
121	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2CH2CO2H
122	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
123	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H
124	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2CH2CO2H
125	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
126	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H
127	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2CH2CO2H
128	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
129	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H
130	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2CH2CO2H
131	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-

					S(O)2CH2CO2H
132	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H
133	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2CH2CO2H
134	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
135	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H

A preferred compounds of the invention or a pharmaceutically acceptable salt or an ester prodrug derivative thereof represented by the formula:



where said compound is selected from a compound code numbered 1A thru 45A, with each compound having the specific selection of substituents R_{B5} and R_{C5} shown in the row following the compound code number, as set out in the following Table 2 :

Table 2

Code No.	R_{B5}	R_{C5}
1A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
2A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
3A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
4A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
5A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
6A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
7A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
8A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H

9A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
10A	3Et3OH-Pentyl	-O-S(O)2Me
11A	3Et3OH-Pentyl	-O-S(O)2Me
12A	3Et3OH-Pentyl	-O-S(O)2Me
13A	3Et3OH-Pentyl	-O-S(O)2Me
14A	3Et3OH-Pentyl	-O-S(O)2Me
15A	3Et3OH-Pentyl	-O-S(O)2Me
16A	3Et3OH-Pentyl	-O-S(O)2Me
17A	3Et3OH-Pentyl	-O-S(O)2Me
18A	3Et3OH-Pentyl	-O-S(O)2Me
19A	3Et3OH-Pentyl	-O-S(O)2Et
20A	3Et3OH-Pentyl	-O-S(O)2Et
21A	3Et3OH-Pentyl	-O-S(O)2Et
22A	3Et3OH-Pentyl	-O-S(O)2Et
23A	3Et3OH-Pentyl	-O-S(O)2Et
24A	3Et3OH-Pentyl	-O-S(O)2Et
25A	3Et3OH-Pentyl	-O-S(O)2Et
26A	3Et3OH-Pentyl	-O-S(O)2Et
27A	3Et3OH-Pentyl	-O-S(O)2Et
28A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
29A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
30A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
31A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
32A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
33A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
34A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
35A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
36A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
37A	3Et3OH-Pentyl	-NH-S(O)2Me
38A	3Et3OH-Pentyl	-NH-S(O)2Me
39A	3Et3OH-Pentyl	-NH-S(O)2Me

40A	3Et3OH-Pentyl	-NH-S(O)2Me
41A	3Et3OH-Pentyl	-NH-S(O)2Me
42A	3Et3OH-Pentyl	-NH-S(O)2Me
43A	3Et3OH-Pentyl	-NH-S(O)2Me
44A	3Et3OH-Pentyl	-NH-S(O)2Me
45A	3Et3OH-Pentyl	-NH-S(O)2Me

Method of Making the Compounds of the Invention:

Compounds of the invention represented by formula (I) may be prepared by the methods set out below. It will be understood by one skilled in the chemical arts that the reactants may be varied to analogous molecules to provide desired substitutions in the final reaction product.

Definitions of symbols used in the Schemes:

(PhO)2P(O)N3 – diphenyl phosphorus azide

BBr3 – boron tribromide

BF3-OEt2 – boron trifluoride etherate

BnBr – benzyl bromide

CH3CN – acetonitrile

DMAP - 4-(dimethylamino)pyridine

DMF – N,N-dimethylformamide

DMSO – dimethylsulfoxide

DPPF – dichloro[1,1'-bis(diphenylphosphino)ferrocene

DPPB – 1,4-bis(diphenylphosphino)butane

EDCI – 3-Ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride

Et3N – triethylamine

EtOH – ethanol

H2NCH2CO2Me – methyl glycinate

HN(OMe)Me – N-methyl-O-methyl hydroxylamine

HNMe2 – dimethyl amine

K2CO3 – potassium carbonate

KOH – potassium hydroxide

LAH – lithium aluminum hydride

LiHMDS – lithium hexamethyldisilazide

mCPBA – meta-chloroperbenzoic acid

MeI – methyl iodide

MeOH – methanol

NaBH4 – sodium borohydride

NaH – sodium hydride

NaI – sodium iodide

NMP - N-methylpyrrolidin-2-one

Na-S-R3 – sodium alkylmercaptide

PBr3 – phosphorus tribromide

Pd(OAc)2 – palladium (II) acetate

Pd-C – palladium on carbon

pTSA – para-toluenesulfonic acid

Pyr - pyridine

R2MgBr – alkyl magnesium bromide

R3MgBr – alkyl magnesium bromide

R5MgBr – alkyl magnesium bromide

R2S(O)2NH2 – alkylsulfonamide

tBuC(O)CH2Br – 2-bromopinacolone

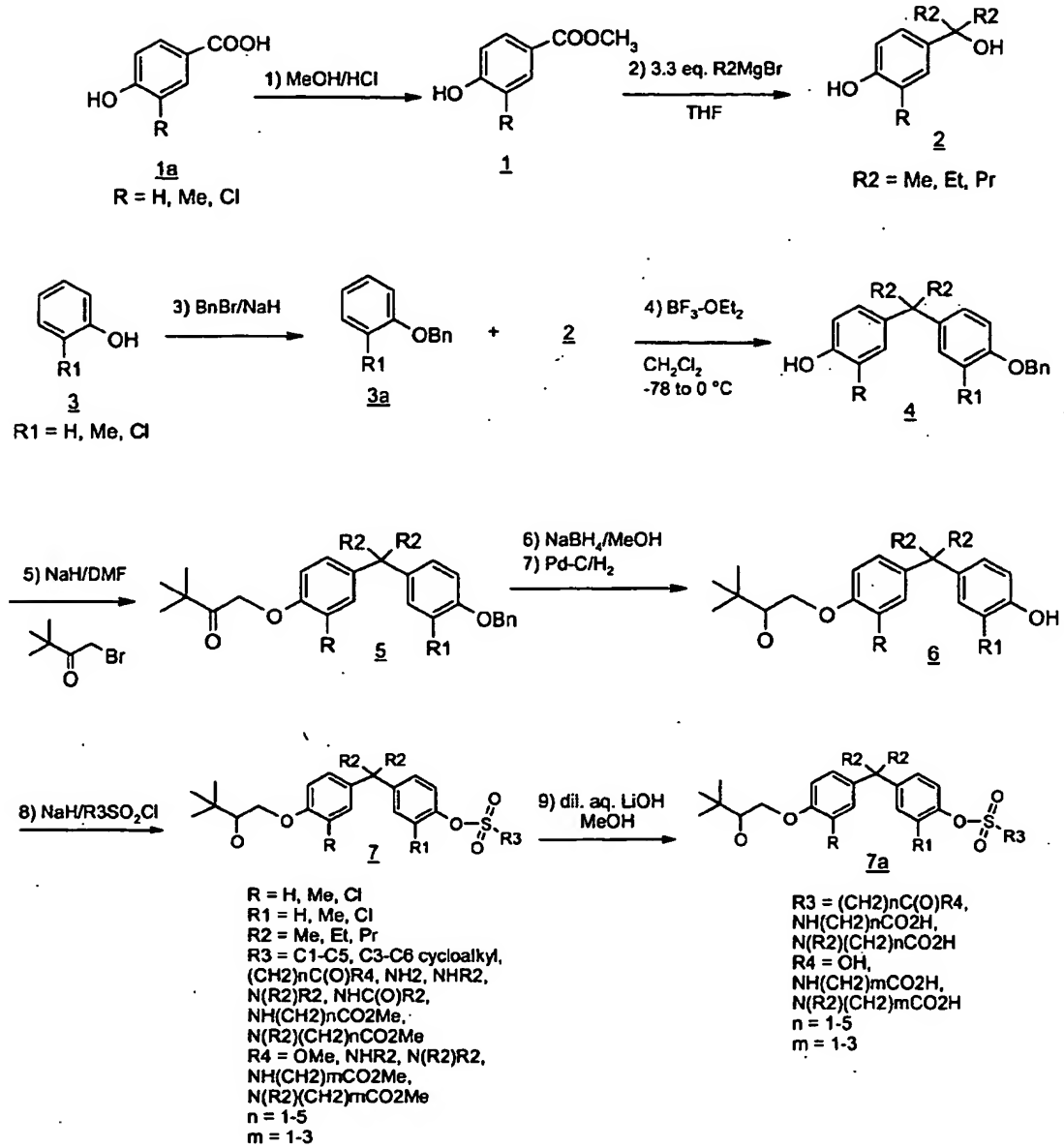
Tf2O – triflic anhydride

TFA – trifluoroacetic acid

THF – tetrahydrofuran

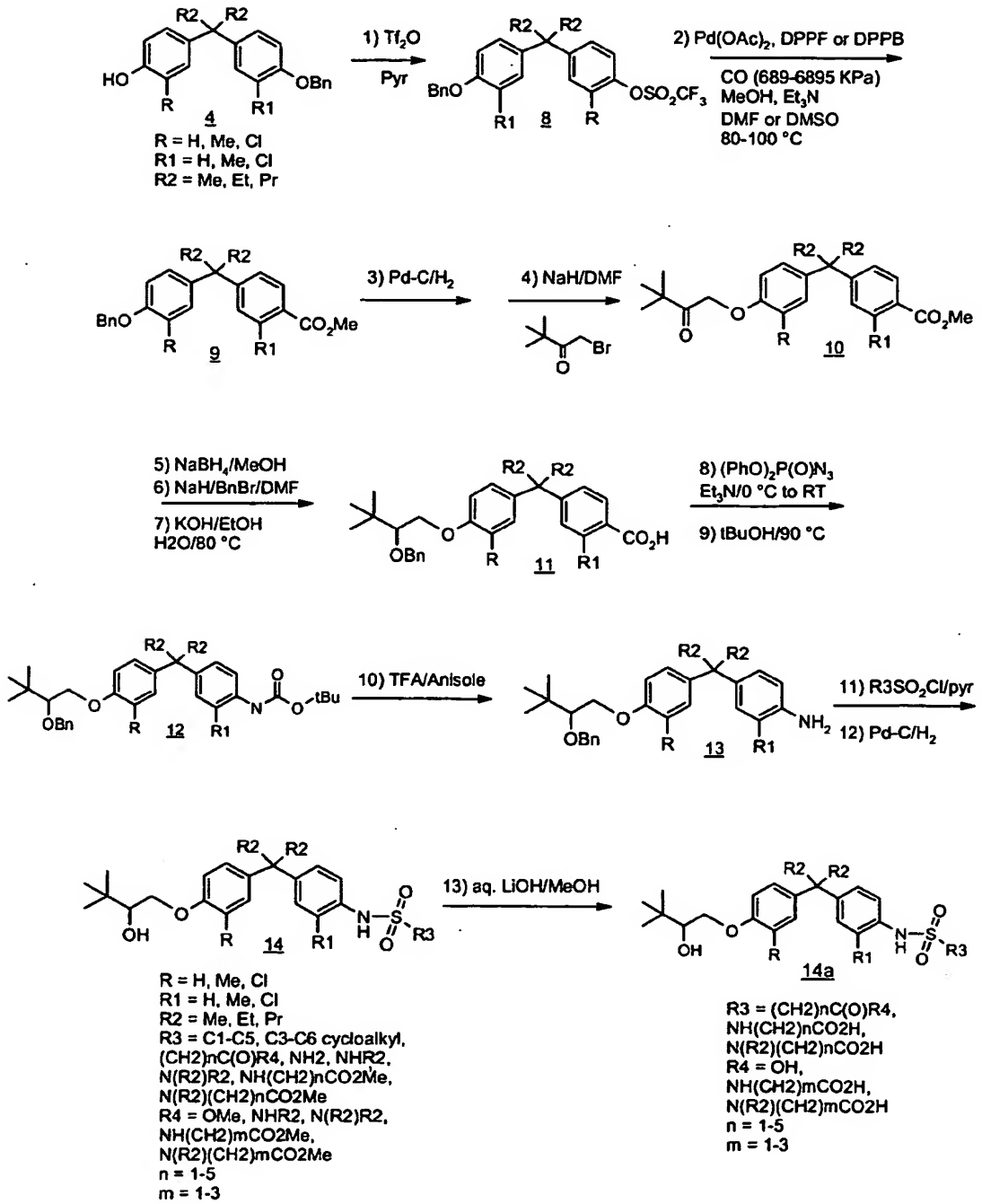
Scheme 1

Synthesis of Phenylalkyl-Phenyl Sulfonates



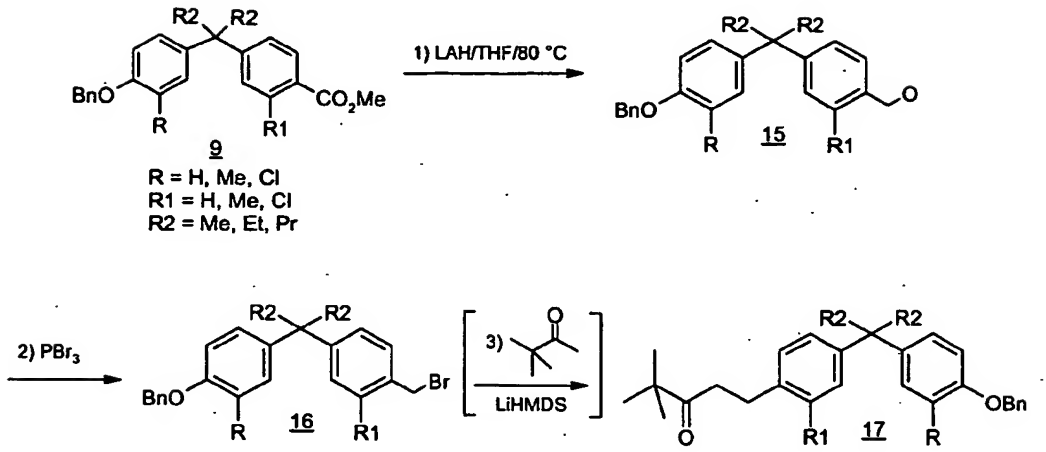
Scheme 2

Synthesis of Phenylalkyl-Phenyl Sulfonamide



Scheme 3

Synthesis of Pentanone Sidechain Analogs



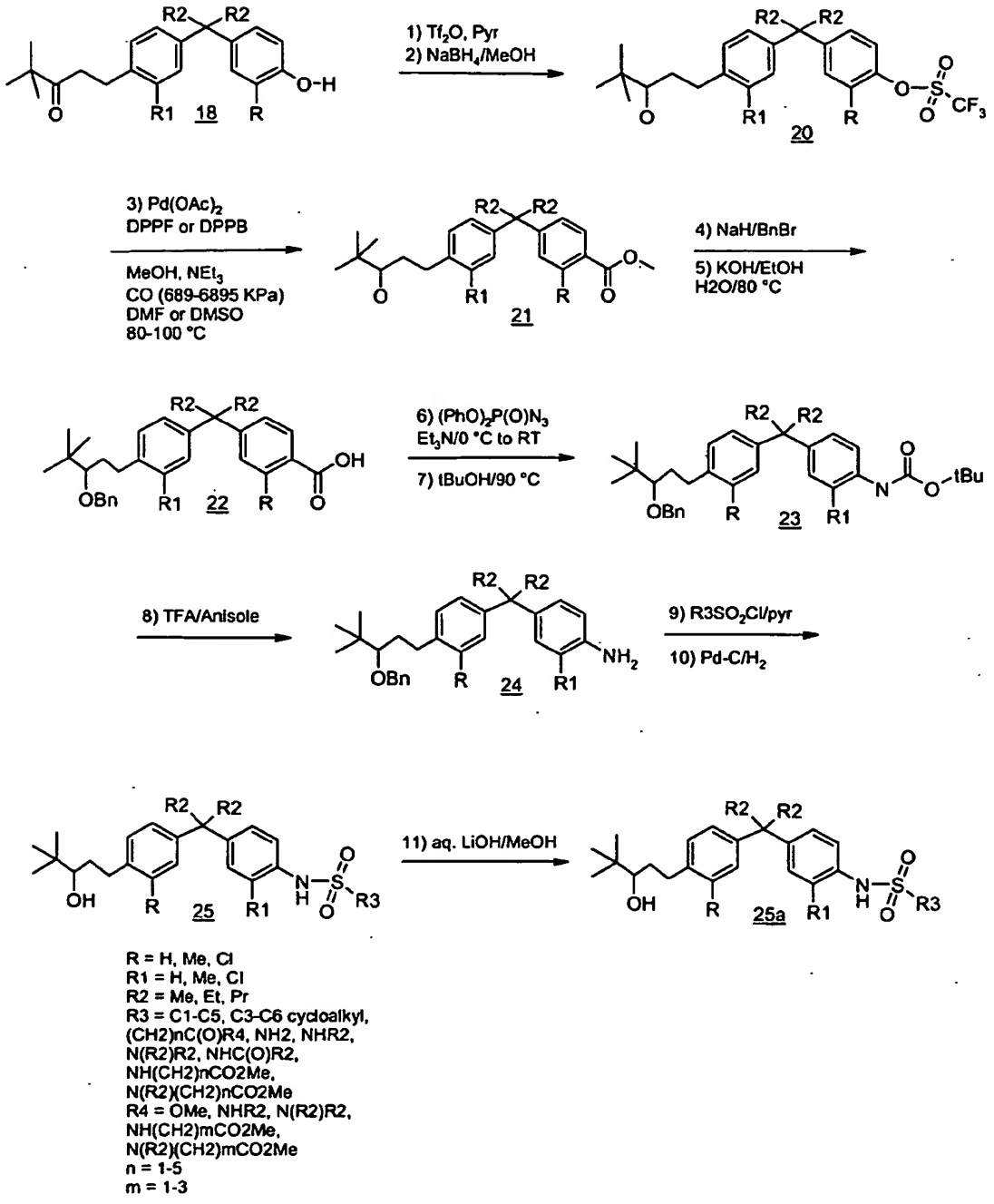
R = H, Me, Cl
R1 = H, Me, Cl
R2 = Me, Et, Pr

R = H, Me, Cl
R1 = H, Me, Cl
R2 = Me, Et, Pr
R3 = C1-C5, C3-C6 cycloalkyl, (CH2)nC(O)R4, NH2, NHR2, N(R2)R2, NHC(O)R2, NH(CH2)nCO2Me, N(R2)(CH2)nCO2Me
R4 = OMe, NHR2, N(R2)R2, NH(CH2)mCO2Me, N(R2)(CH2)mCO2Me
n = 1-5
m = 1-3

R3 = (CH2)nC(O)R4, NH(CH2)nCO2H, N(R2)(CH2)nCO2H
R4 = OH, NH(CH2)mCO2H, N(R2)(CH2)mCO2H
n = 1-5
m = 1-3

Scheme 4

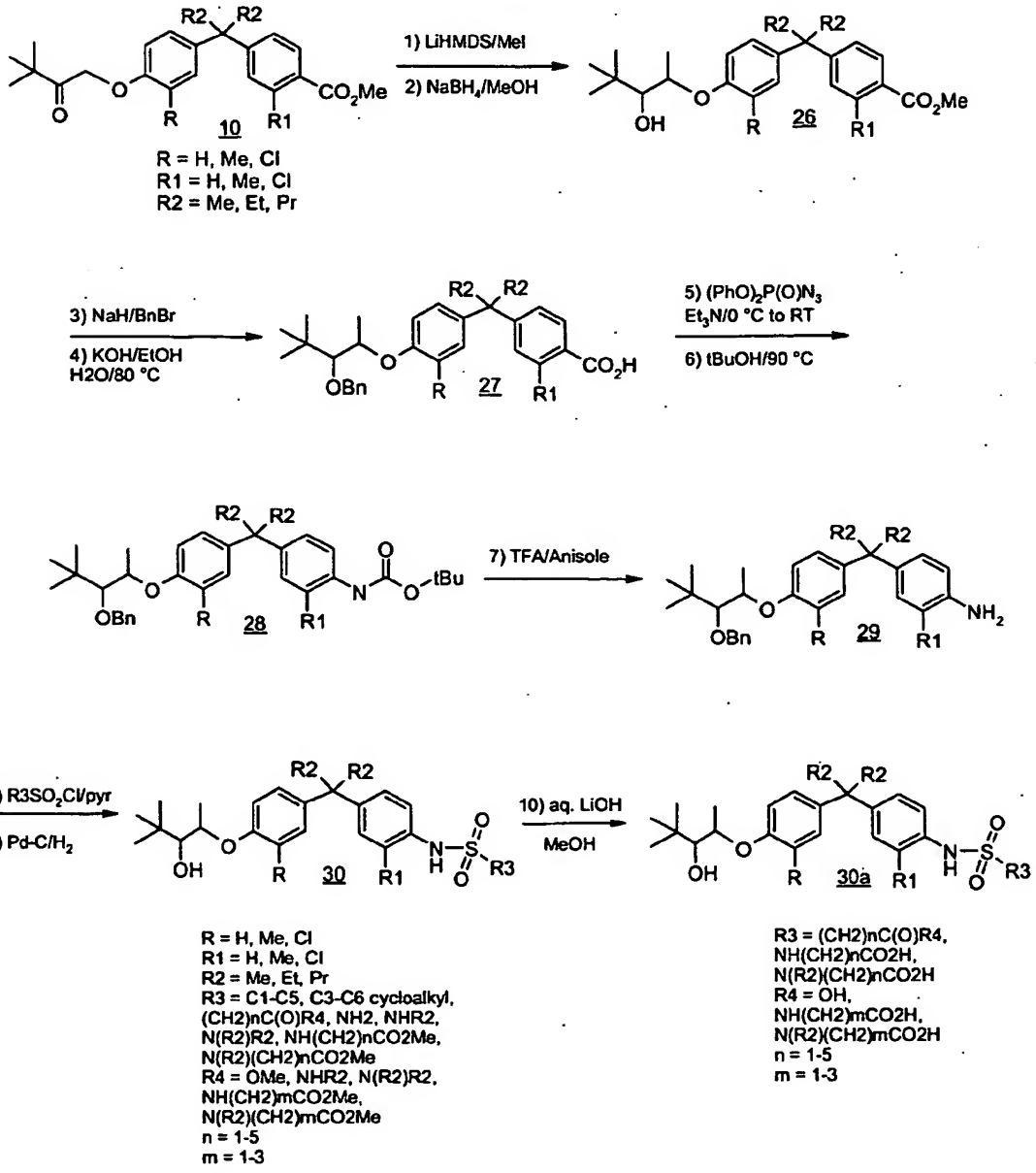
Synthesis of Pentanone/Sulfonamide Analogs



R = H, Me, Cl
R1 = H, Me, Cl
R2 = Me, Et, Pr
R3 = C1-C5, C3-C6 cycloalkyl, (CH2)nC(O)R4, NH2, NHR2, N(R2)R2, NHC(O)R2, NH(CH2)nCO2Me, N(R2)(CH2)nCO2Me
R4 = OMe, NHR2, N(R2)R2, NH(CH2)mCO2Me, N(R2)(CH2)mCO2Me
n = 1-5
m = 1-3

Scheme 5

Synthesis of Methylated Pinacolol Sidechain-Sulfonamides



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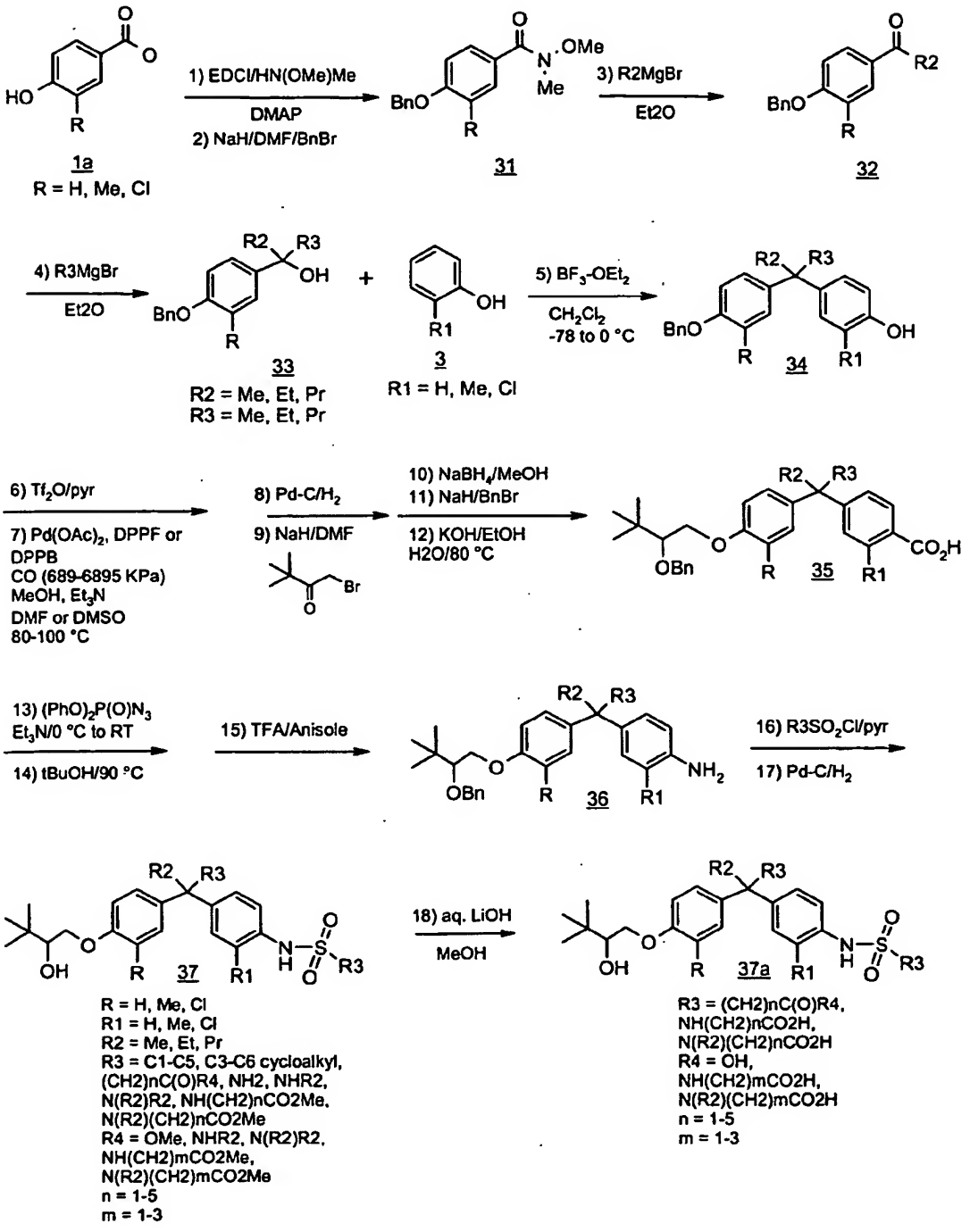
Scheme 6

Synthesis of Unsymmetrical Central Linked Phenylalkyl-Phenyl Scaffold



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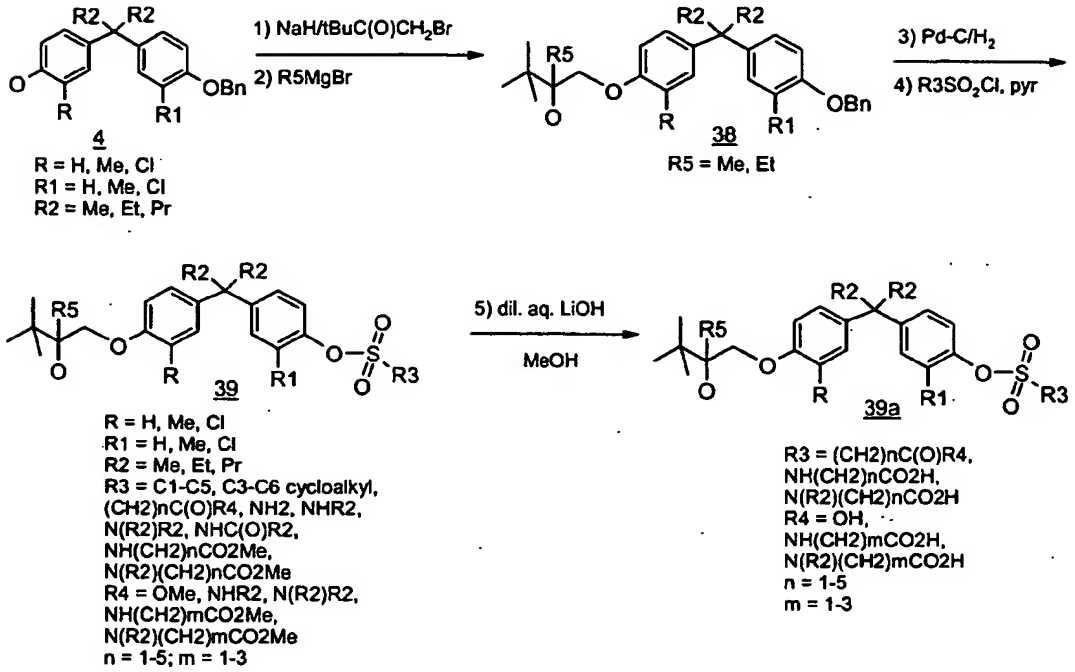
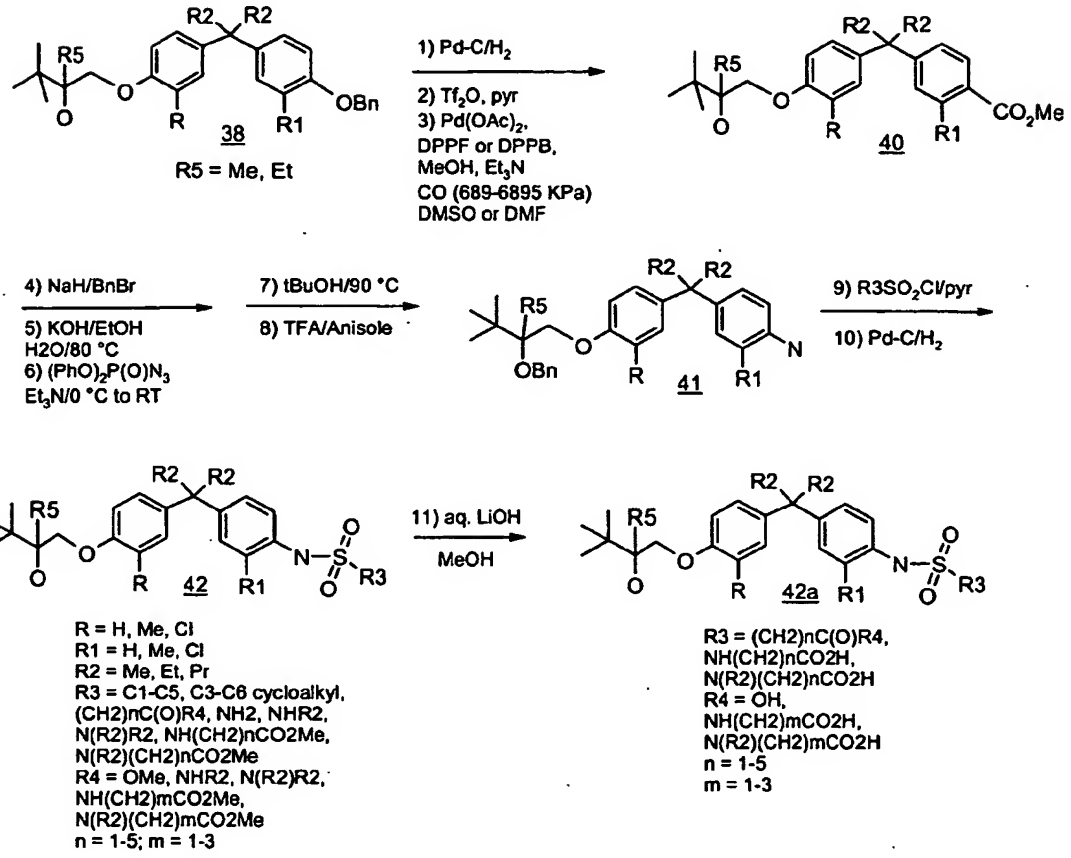
Scheme 7

Synthesis of Tertiary Alcohol-Sulfonate Sidechain



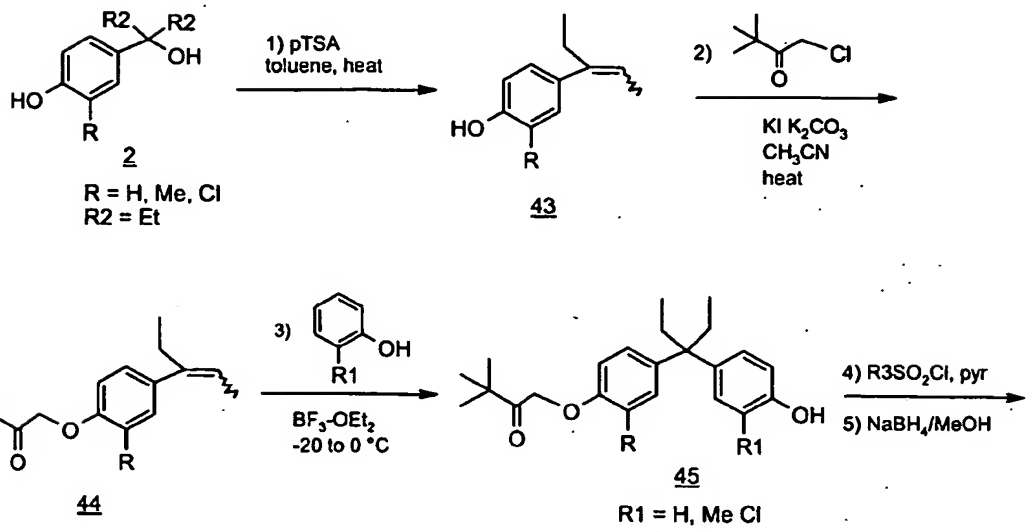
Scheme 8

Synthesis of Tertiary Alcohol-Sulfonamide Sidechain

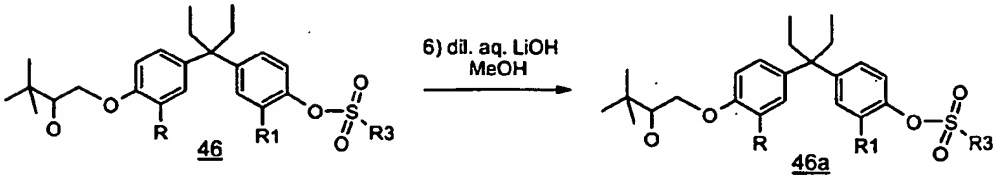


Scheme 9

Alternative Synthesis of Phenylalkyl-Phenyl Scaffold



R1 = H, Me Cl



R = H, Me, Cl
R1 = H, Me, Cl
R2 = Me, Et, Pr
R3 = C1-C5, C3-C6 cycloalkyl, (CH2)nC(O)R4, NH2, NHR2, N(R2)R2, NHC(O)R2, NH(CH2)nCO2Me, N(R2)(CH2)nCO2Me
R4 = OMe, NHR2, N(R2)R2, NH(CH2)mCO2Me, N(R2)(CH2)mCO2Me
n = 1-5
m = 1-3

R3 = (CH2)nC(O)R4, NH(CH2)nCO2H, N(R2)(CH2)nCO2H
R4 = OH, NH(CH2)mCO2H, N(R2)(CH2)mCO2H
n = 1-5
m = 1-3

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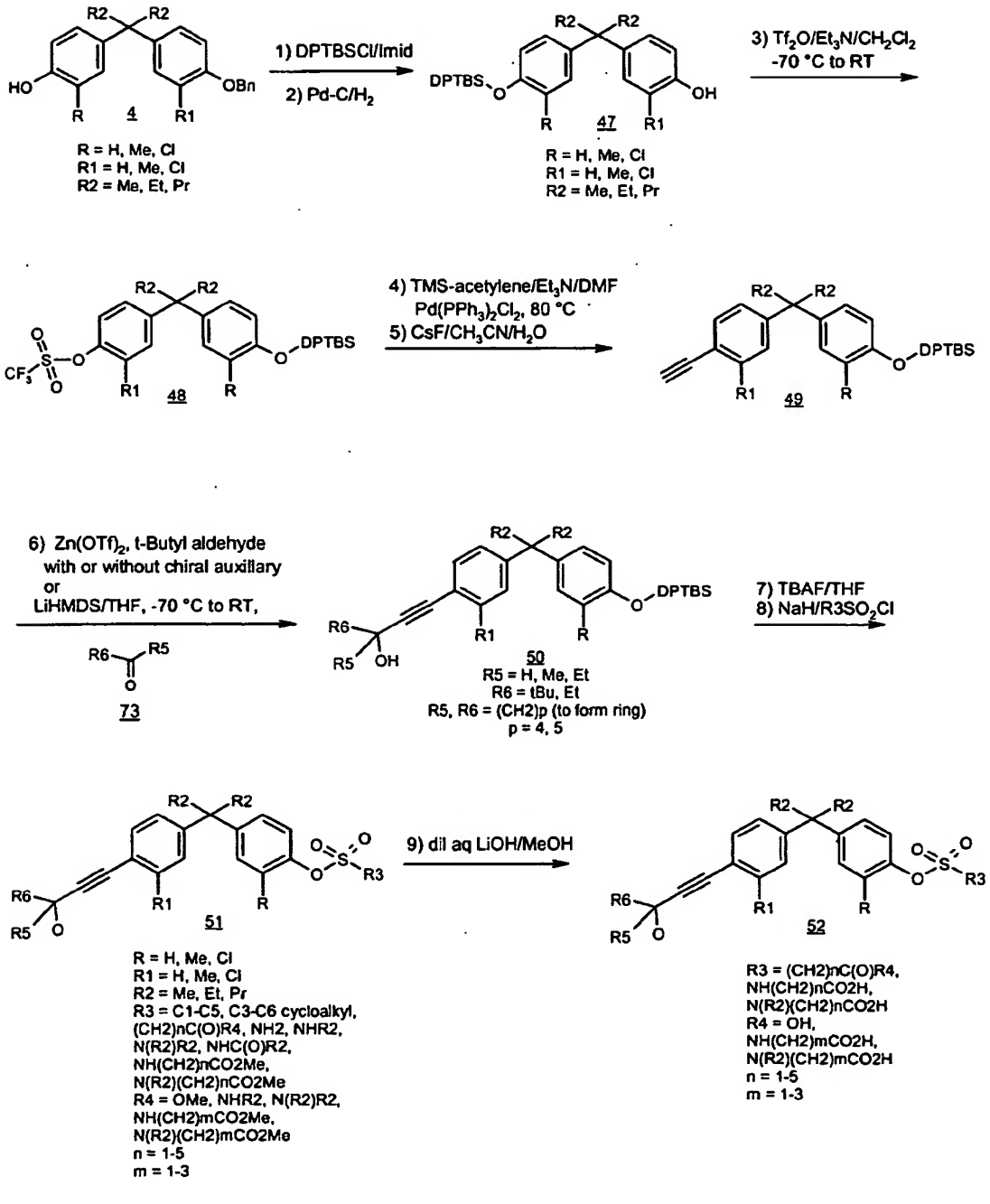
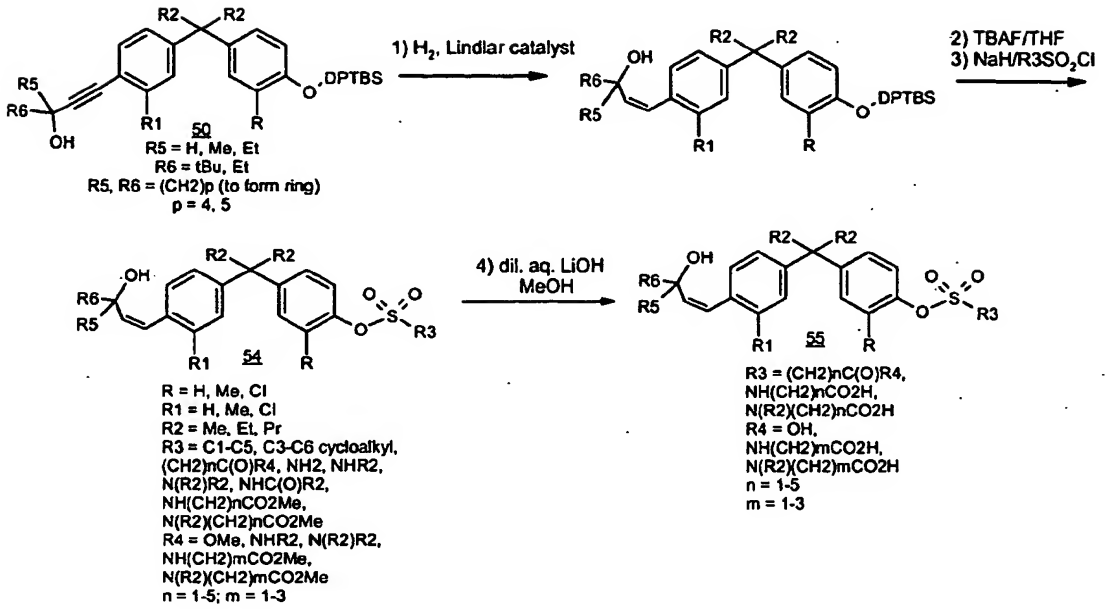
Scheme 10

Synthesis of Pentynol - Sulfonate Analogs



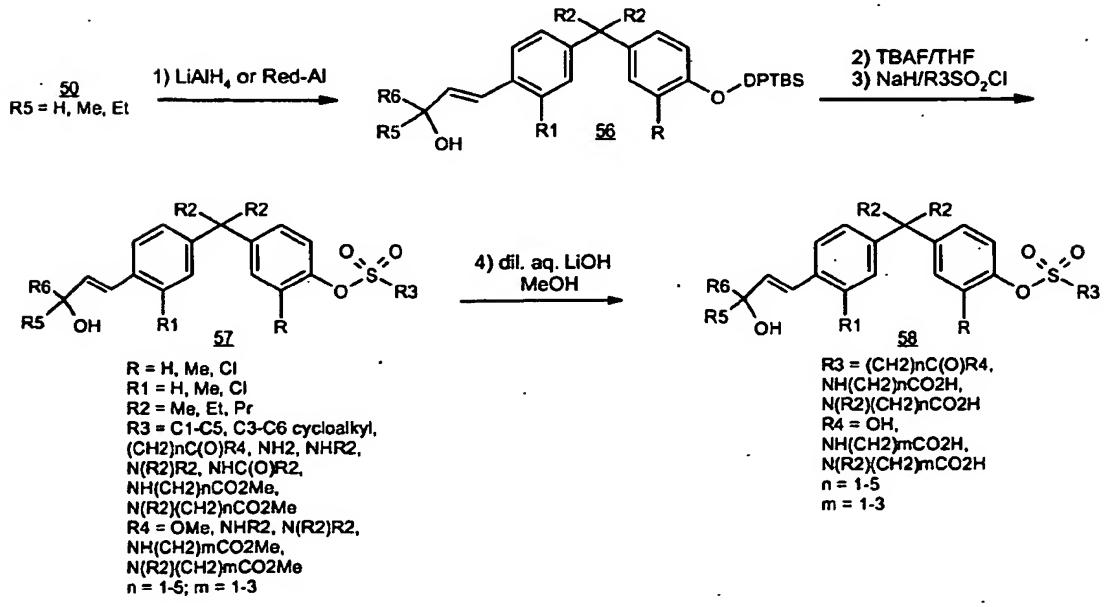
Scheme 11

Synthesis of Cis- Pentenol - Sulfonate Analogs



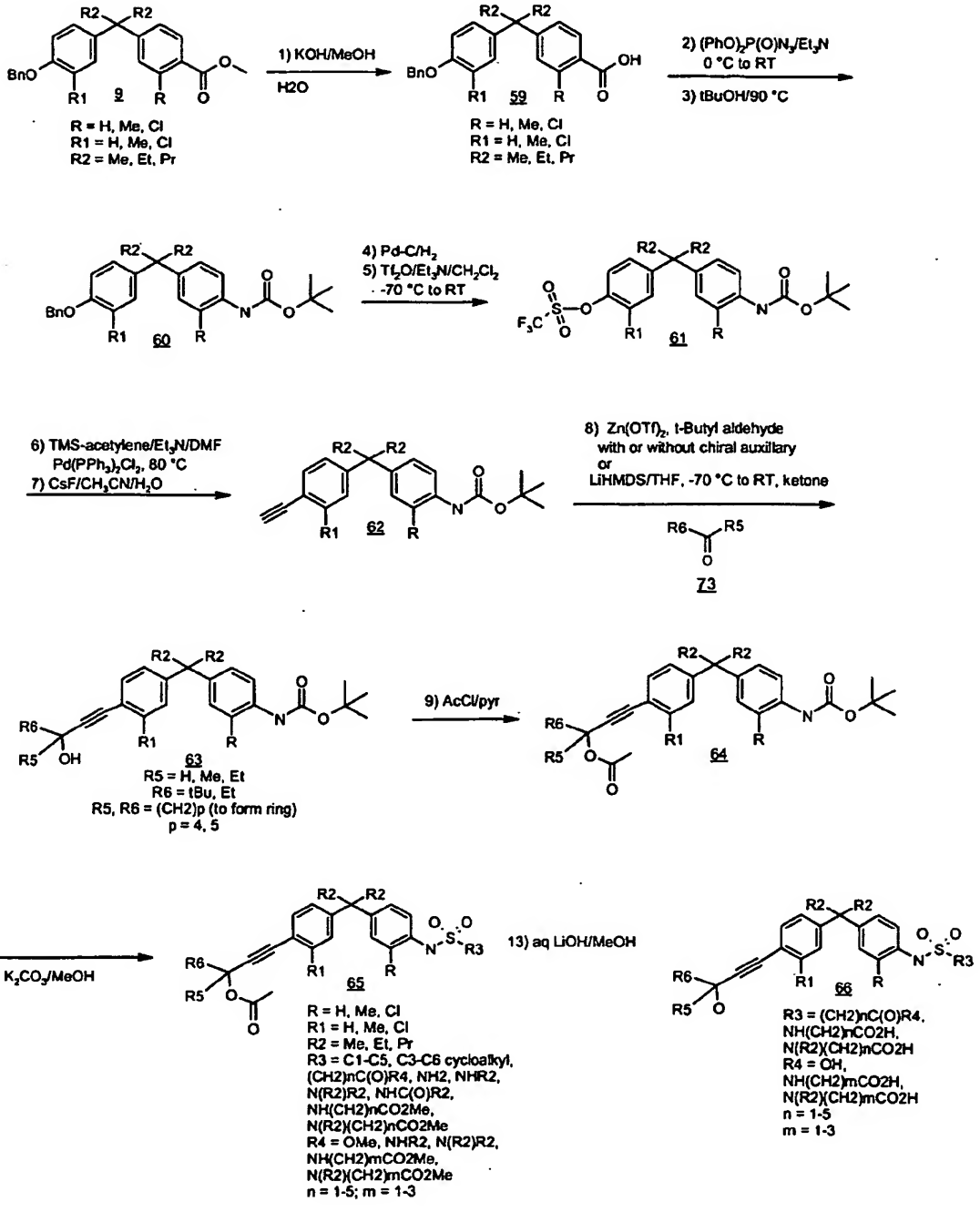
Scheme 12

Synthesis of Trans- Pentenol - Sulfonate Analogs



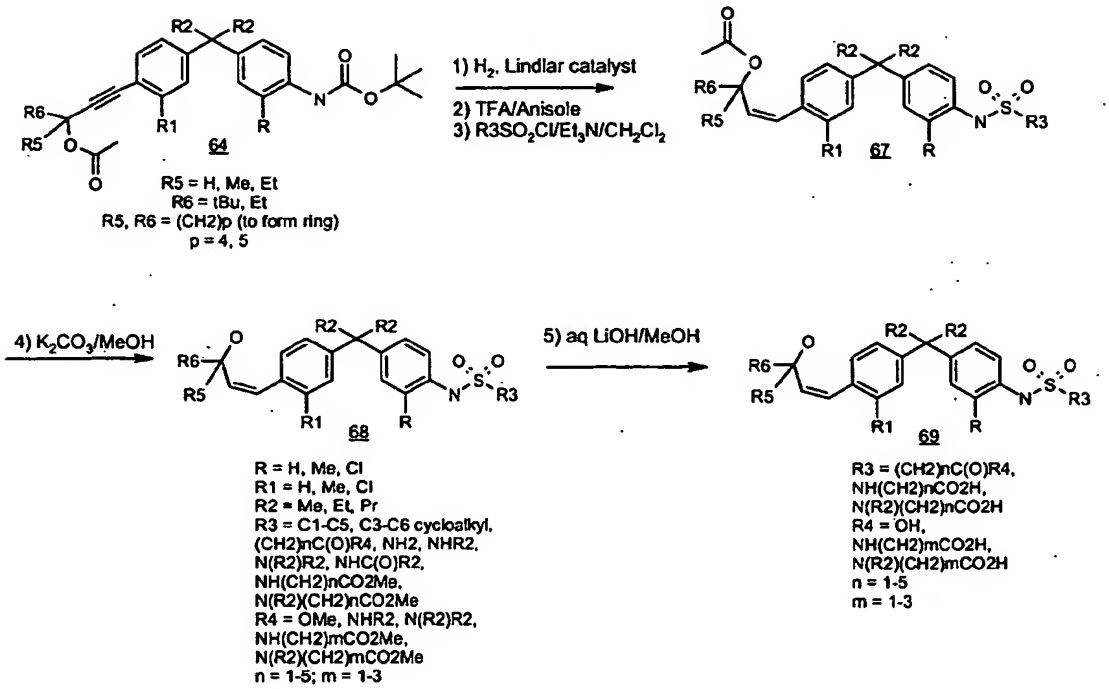
Scheme 13

Synthesis of Pentynol - Sulfonamide Analogs



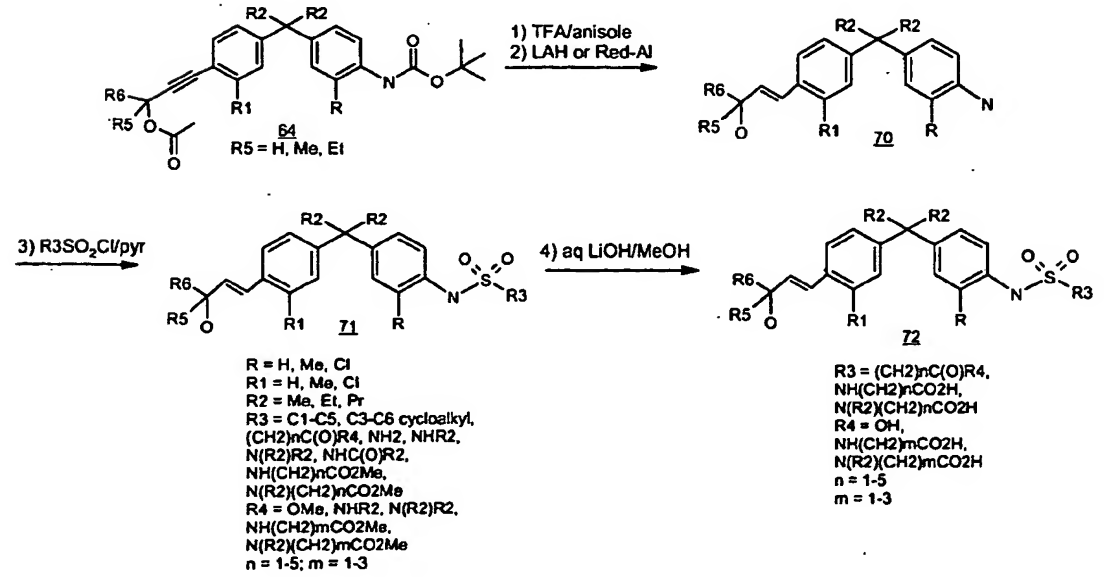
Scheme 14

Synthesis of Cis-Pentenol - Sulfonamide Analogs



Scheme 15

Synthesis of Trans-Pentenol - Sulfonamide Analogs



Preparation of phenylalkyl-phenyl sulfonates (Scheme 1).

A mixture of 3-substituted-4-hydroxy benzoic acid 1a and methanol is treated with HCl (gas) to yield methyl benzoate ester 1. Methyl benzoate ester 1 is reacted with excess alkyl magnesium bromide to produce tertiary alcohol 2. Tertiary alcohol 2 is converted to phenol 4 by reaction with O-benzyl-2-substituted phenol 3a and BF3-Et2O. O-benzyl-2-substituted phenol 3a is derived from reaction of 2-substituted phenol 3 with benzylbromide and NaH. Phenol 4 is reacted with NaH/1-bromopinacolone to give ketone 5. Ketone 5 is reduced with NaBH4 and hydrogenolyzed with Pd-C/H2 to give alcohol-phenol 6. Alcohol-phenol 6 is reacted with a sulfonyl chloride to give a sulfonyl derivative 7. Sulfonyl derivative 7 is hydrolyzed with aq. LiOH/MeOH to give sulfonyl-acid derivatives 7a.

Preparation of phenylalkyl-phenyl sulfonamides (Scheme 2).

Phenol 4 is reacted with triflic anhydride/pyridine to give triflate 8 which is subjected to methoxycarbonylation with Pd(OAc)2, DPPF (or DPPB), CO (689-6895 KPa), methanol and triethylamine in either DMF or DMSO at 80-100 °C to yield methyl ester 9. Methyl ester 9 is subjected to palladium catalyzed hydrogenolysis and alkylated with NaH/1-bromopinacolone to give ketone 10. Ketone 10 is sequentially reacted with sodium borohydride/MeOH, NaH/BnBr, and potassium hydroxide/EtOH/H2O/80 °C to produce acid 11. Acid 11 is reacted with (PhO)2P(O)N3/Et3N and heated with t-BuOH at 90 C to give BOC-amine 12. Boc-amine 12 is reacted with TFA/anisole to give amine 13. Amine 13 is reacted with a sulfonyl chloride/pyridine and Pd-C/H2 to afford sulfonamide 14. Sulfonamide 14 is reacted with aq. LiOH/MeOH to give sulfonamide 14a.

Preparation of pentanone sidechain analogs (Scheme 3).

Ester 9 is reduced with LAH to give benzyl alcohol 15. Benzyl alcohol 15 is converted to benzylic bromide 16 with PBr3 and alklylated with the lithium enolate of pinacolone to afford ketone 17. Ketone 17 is reacted with Pd-C/H2 to afford alcohol 18. Alcohol 18 is sulfonated with an alkyl sulfonyl chloride/pyridine and reduced with NaBH4/MeOH to give sulfonate 19. Sulfonate 19 is reacted with aq. LiOH/MeOH to produce sulfonamide 19a.

Preparation of pentanone/sulfonamide analogs (Scheme 4).

Ketone phenol 18 is reacted with triflic anhydride/pyridine and NaBH4/MeOH to give triflate 20. Triflate 20 is subjected to methoxycarbonylation with Pd(OAc)2, DPPF (or DPPB), CO (689-6895 KPa), methanol and triethylamine in either DMF or DMSO at 80-100 °C to yield methyl ester 21. Methyl ester 21 is reacted with NaH/BnBr and potassium hydroxide/EtOH/H2O/80 °C to produce acid 22. Acid 22 is reacted with (PhO)2P(O)N3/Et3N and heated with t-BuOH at 90 °C to give BOC-amine 23. BOC-amine 23 is reacted with TFA/anisole to give amine 24. Amine 24 is reacted with a sulfonyl chloride/pyridine and Pd-C/H2 to give sulfonamide 25. Sulfonamide 25 is reacted with aq. LiOH/MeOH to give sulfonamide 25a.

Preparation of methylated pinacolol sidechain-sulfonamides (Scheme 5).

Ketone 10 is reacted with LiHMDS/MeI and NaBH4/MeOH to give ester 26. Ester 26 is reacted with KOH/EtOH/H2O/80 °C, (PhO)2P(O)N3/Et3N and heated with t-BuOH at 90 °C to give BOC-amine 28. BOC-amine 28 is reacted with TFA/anisole to give amine 29. Amine 29 is reacted with a sulfonyl chloride/pyridine and Pd-C/H2 to give sulfonamide 30. Sulfonamide 30 is reacted with aq. LiOH/MeOH to afford sulfonamide 30a.

Preparation of unsymmetrical central link phenylalkyl-phenyl scaffold (Scheme 6).

3-Substituted-4-hydroxy benzoic acid 1a is reacted with EDCI/HN(OMe)Me/DMAP and NaH/BnBr to give amide 31. Amide 31 is reacted sequentially with a R2MgBr and R3MgBr to give alcohol 33. Alcohol 33 is treated with phenol 3 and BF3-OEt2 to give phenol 34. Phenol 34 is sequentially reacted with: 1) triflic anhydride/pyridine; 2) Pd(OAc)2, DPPF (or DPPB), CO (689-6895 KPa), methanol and triethylamine in either DMF or DMSO at 80-100 °C; 3) Pd-C/H2; 4) NaH/1-bromopinacolone; 5) NaBH4/MeOH; 6) NaH/BnBr; and 7) KOH/EtOH/H2O/80 °C to give acid 35. Acid 35 is reacted with (PhO)2P(O)N3/Et3N, heated with t-BuOH at 90 °C, and TFA/anisole to give amine 36. Amine 36 is reacted with a sulfonyl chloride/pyridine and Pd-C/H2 to afford sulfonamide 37. Sulfonamide 37 is reacted with aq. LiOH/MeOH to give sulfonamide 37a.

Preparation of tertiary alcohol-sulfonate sidechain (Scheme 7).

Phenol 4 is reacted with NaH/1-bromopinacolone and R5MgBr to give alcohol 38 Alcohol 38 is treated with Pd-C/H2 and a sulfonyl chloride/pyridine to give sulfonate 39 Sulfonamide 39 is reacted with aq. LiOH/MeOH to give sulfonamide 39a.

Preparation of tertiary alcohol-sulfonamide sidechain (Scheme 8).

Alcohol 38 is reacted with Pd-C/H2, triflic anhydride/pyridine and Pd(OAc)2, DPPF (or DPPB), CO (689-6895 KPa), methanol and triethylamine in either DMF or DMSO at 80-100 °C to give ester 40. Ester 40 is reacted sequentially with: 1) NaH/BnBr; 2) KOH/EtOH/H2O; 3) (PhO)2P(O)N3/Et3N; 4) heated with t-BuOH at 90 °C; and 5) TFA/anisole to give amine 41. Amine 41 is reacted with a sulfonyl chloride/pyridine and Pd-C/H2 to afford sulfonamide 42. Sulfonamide 42 is treated with aq. LiOH/MeOH to give sulfonamide-acids 42a.

Alternative preparation of phenylalkyl-phenyl scaffold (Scheme 9).

Phenol 2 is reacted with pTSA/heat to give a mixture of e/z olefin 43. Olefin 43 is reacted with 1-chloropinacolone/KI/K2CO3 to give ketone 44. Ketone 44 is reacted with a substituted phenol 3 and BF3-OEt3 to give phenol 45. Phenol 45 is reacted with a sulfonyl chloride/pyridine and NaBH4/MeOH to give sulfonate 46. Sulfonate 46 is reacted with aq. LiOH/MeOH to give sulfonate-acids 46a.

Preparation of pentynol-sulfonate analogs (Scheme 10).

Phenol 4 is reacted with DPTBSCl/Imid and Pd-C/H2 to give silyl ether-phenol 47. Silyl ether-phenol 47 is reacted with triflic anhydride/pyridine to give triflate 48. Triflate 48 is reacted with TMS-acetylene/Et3N/Pd(PPh3)2Cl2 at 80 °C and CsF/H2O to give acetylene 49. Acetylene 49 is treated with Zn(OTf)2/t-butyl aldehyde/chiral auxiliary (with or without) to give alcohol 50. Alternatively, acetylene 49 is reacted with LiHMDS/ketone 73 to give alcohol 50. Alcohol 50 is reacted with TBAF and NaH/R3SO2Cl to give sulfonate 51. Sulfonate 51 is reacted with aq. LiOH/MeOH to give sulfonate-acids 52.

Preparation of cis-pentenol-sulfonate analogs (Scheme 11).

Alcohol 50 is reacted with Lindlar catalyst/H2 to give cis-olefin 53. Cis-olefin 53 is reacted with TBAF and NaH/R3SO2Cl to give sulfonate 54. Sulfonate 54 is reacted with dilute aq. LiOH/MeOH to give sulfonate-acids 55.

Preparation of trans-pentenol-sulfonate analogs (Scheme 12).
Alcohol 50 is reacted with LAH or Red-Al to give trans-olefin 56. Trans-olefin 56 is reacted with TBAF and NaH/a sulfonyl chloride to give sulfonate 57. Sulfonate 57 is reacted with dilute aq LiOH/MeOH to give sulfonate-acids 58.

Preparation of pentynol-sulfonamide analogs (Scheme 13).
Ester 9 is reacted with KOH/MeOH to give acid 59. Acid 59 is treated with (PhO)2P(O)N3/Et3N and heated with t-BuOH at 90 C to give Boc-amine 60. Boc-amine 60 is reacted with Pd-C/H2 and triflic anhydride/Et3N to give triflate 61. Triflate 61 is reacted with TMS-acetylene/Et3N/Pd(PPh3)2Cl2 at 80 °C and CsF/H2O to give acetylene 62. Acetylene 62 is treated with Zn(OTf)2/t-butyl aldehyde/chiral auxiliary (with or without) to give alcohol 63. Alternatively, Acetylene 62 is reacted with LiHMDS/ketone 73 to give alcohol 63. Alcohol 63 is reacted with acetyl chloride to give acetate 64. Acetate 64 is reacted with TFA/anisole, a sulfonyl chloride/Et3N, and K2CO3/MeOH to give amine 65. Amine 65 is reacted with aq LiOH/MeOH to give a sulfonamide 66.

Preparation of cis-pentenol-sulfonamide analogs (Scheme 14).
Acetate 64 is reacted with Lindlar's catalyst/H2, TFA/anisole, and a sulfonyl chloride/Et3N to give sulfonamide 67. Sulfonamide 67 is reacted with K2CO3/MeOH to give alcohol 68. Alcohol 68 is reacted with aq. LiOH/MeOH to give sulfonamide 69.

Preparation of trans-pentenol-sulfonamide analogs (Scheme 15).
Acetate 64 is reacted with TFA/anisole and LAH to give trans-pentenol 70. Trans-pentenol is reacted with a sulfonyl chloride/Et3N to give sulfonamide 71. Sulfonamide 71 is reacted with aq. LiOH/MeOH to give sulfonamide 72.

EXAMPLES

General Experimental Conditions:

The starting material/intermediate is the compound from the immediate preceding experimental unless otherwise indicated.

All reactions are performed under nitrogen/argon atmosphere, in a stirred reaction vessel, and at room temperature unless indicated otherwise.

Concentration is performed from RT to about 70°C under vacuum (0.05 to 1 mm Hg).

Unless otherwise indicated, the organic layer is MgSO4/Na2SO4 dried is defined as stirring the solution with a dessicant for 5-15 m and filtering off the dessicant to give an anhydrous filtrate.

For analogous multi-step reaction procedures, the yield is given either for the ultimate step or overall multi-steps as indicated.

Solutions are "concentrated" at a range of 25-75°C with reduced pressure.

in-vacuo – 25-75°C; 0.05 to 1 mm

Unless otherwise indicated, "the residue is chromatographed" is defined as silica gel chromatography of residue with moderate nitrogen pressure (flash chromatography) or a medium pressure chromatography systems using a silica gel to crude product ratio of ~10-100.

Thin layer chromatography is performed with silica gel plates with UV and/or appropriate staining solution.

NMR spectra are obtained with either 300 or 400 mHz spectrometer.

NMR – denotes NMR spectrum is consistent with assigned structure.

HRMS – high resolution mass spectrum

ES-MS – electrospray mass spectrum

Abbreviations:

Aq - aqueous

d – day

eq - equivalent

h – hour

m – minute

satd – saturated

disp – dispersion

quant – quantitative

rt for retention time (both small caps to minimize confusion with RT)

RT – room temperature

Chemical Definitions:

BBr3 – boron tribromide

BF3-OEt2 – boron trifluoride etherate

BnBr – benzyl bromide

CH2Cl2-dichloromethane

CH3CN – acetonitrile

CO-carbon monoxide

Dess-Martin reagent – 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one

DIBAlH - Diisobutyl Aluminum Hydride

DMAP - 4-(dimethylamino)pyridine

DMF – N,N-dimethylformamide

DMSO – dimethylsulfoxide

DPPB – 1,4-bis(diphenylphosphino)butane

DPPF – dichloro[1,1'-bis(diphenylphosphino)ferrocene

EDCI – 3-Ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride

Et3N – triethylamine

EtMgBr- ethyl magnesium bromide

EtOAc – ethyl acetate

EtOH – ethanol

H2NCH2CO2Me – methyl glycinate

Hept – heptane

Hex - hexanes

HN(OMe)Me – N-methyl-O-methyl hydroxylamine

HNMe2 – dimethyl amine

HATU – O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HOAT – 7-aza-1-hydroxybenzotriazole

HOBT – 1-hydroxybenzotriazole

K2CO3 – potassium carbonate

KOH – potassium hydroxide

LAH – lithium aluminum hydride

LiHMDS – lithium hexamethyldisilazide

mCPBA – meta-chloroperbenzoic acid

MeI – methyl iodide

MeOH – methanol

NaBH4 – sodium borohydride

MgSO4- magnesium sulfate

NaH – sodium hydride

NaHCO3-sodium bicarbonate

NaI – sodium iodide

Na2SO4- sodium sulfate

NH4Cl- ammonium chloride

NMO – 4-methylmorpholine N-oxide

NMP - N-methylpyrrolidin-2-one

Na-S-R3 – sodium alkylmercaptide

PBr3 – phosphorus tribromide

Pd(DPPF) - palladium dichloro[1,1'-bis(diphenylphosphino)ferrocene

Pd(OAc)2 – palladium (II) acetate

Pd(TPP)4 – palladium tetrakistriphenylphosphine

Pd-C – palladium on carbon

(PhO)2P(O)N3 – diphenyl phosphorus azide

pTSA – para-toluenesulfonic acid

Pyr – pyridine

Red-Al – sodium bis(2-methoxyethoxy)aluminum hydride

R2MgBr – alkyl magnesium bromide

R3MgBr – alkyl magnesium bromide

R5MgBr – alkyl magnesium bromide

R2S(O)2NH2 – alkylsulfonamide

TBAF- tetrabutylammonium fluoride

TBSCl- *tert*-butyldimethylsilyl chloride

tBuC(O)CH2Br – 1-bromopinacolone

Tf2O – triflic anhydride

TFA – trifluoroacetic acid

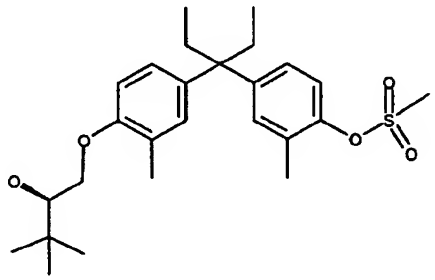
THF – tetrahydrofuran

TPAP – tetrapropylammonium perruthenate

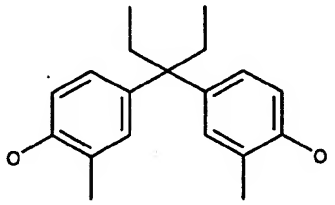
Zn(OTf)2 – zinc trifluoromethane sulfonate.

Example 1

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(methanesulfonyloxy)-3-methylphenyl]pentane.



A. 3',3'-Bis[4-hydroxy-3-methylphenyl]pentane .

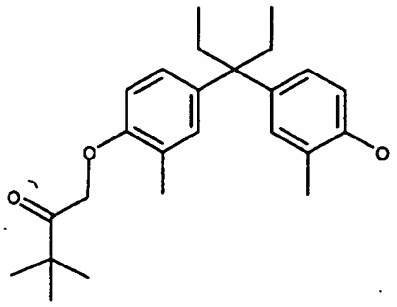


To a mixture of o-cresol (196 g, 1.81 mol) and 3-pentanone (60 ml, 0.57 mol) is added $MeSO_3H$ (45 ml, 0.69 mol) and stirred for 3 d. The reaction is carefully basified to pH 8 with satd Na_2CO_3 and extracted with EtOAc. The organic layer is washed with water (6 X 500 ml), Na_2SO_4 dried, concentrated, chromatographed (2 kg SiO_2, Hex to 80% EtOAc/Hex), and triturated with Hex to give the title compound as a white solid (100 g, 61%).

NMR 400 mHz(DMSO): δ 0.49 (t, J = 7.3 Hz, 6H), 1.91 (q, J = 7.3 Hz, 4H), 2.02 (s, 6H), 6.61 (d, J = 8.3 Hz, 2H), 6.73 (d, J = 8.3 Hz, 2H), 6.76 (s, 2H), 8.94 (s, 2H).

High Res. EI-MS: 284.1794; calc. for $C_{19}H_{24}O_2$: 284.1776

B. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl)]-3'-[4-hydroxy-3-methylphenyl]pentane .



To a mixture of 60% NaH disp (8.0 g, 200 mmol) and DMF (600 ml) is added 3,3-bis[4-hydroxy-3-methylphenyl]pentane (56.88 g, 200 mmol) and stirred for 2 h. The reaction is added 3,3-dimethyl-1-bromo-2-butanone (26.93 ml, 200 mmol) dropwise and stirred overnight. The solvent is removed in-vacuo. The resulting residue is added EtOAc/water (800 ml/200 ml), acidified to pH 3 with 5N HCl, and partitioned. The organic layer is washed with water (2X), brine, Na_2SO_4 dried, concentrated, and chromatographed (3 kg SiO_2, Hex to 15% EtOAc/Hex) to give the title compound as a white solid (35 g, 46%).

NMR (300mHz, DMSO): δ 0.52 (t, J = 7.3 Hz, 6H), 1.16 (s, 9H), 1.95 (q, J = 7.3 Hz, 4H), 2.04 (s, 3H), 2.12 (s, 3H), 5.05 (s, 2H), 6.57 (d, J = 9.1 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.81 (m, 2H), 8.97 (s, 1H).

ES-MS: 400(M+NH4).

C. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-hydroxy-3-methylphenyl]pentane

To a 0 °C mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl)]-3'-[4-hydroxy-3-methylphenyl]pentane (7.3 g, 19.1 mmol) and methanol (75 ml) is added $NaBH_4$ (1.58 g, 42.6 mmol) in portions. After 2 h, the reaction is warmed to RT and stirred overnight. The reaction is quenched with 1N HCl and then concentrated in-vacuo. The mixture is partitioned between Et_2O/water. The organic layer is washed with water, Na_2SO_4 dried, and concentrated to give the title compound as a glassy solid (7.2 g, 98%).

NMR

High Res. ES-MS: 402.3010; calc. for $C_{25}H_{40}NO_3$: 402.3008

D. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methanesulfonyloxy-3-methylphenyl]pentane

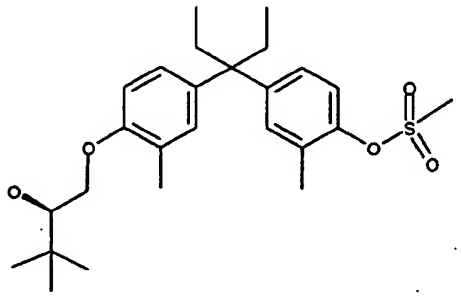
To a mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-hydroxy-3-methylphenyl]pentane (150 mg, 0.39 mmol) and DMF (1.5 ml) is added 60% NaH disp (16.4 mg, 0.41 mmol). After stirring for 5 m, the reaction is added mesyl chloride (33 ul, 0.43 mmol) and heated to 80 °C for 5 h. The reaction is concentrated in-vacuo and partitioned between Et_2O/water. The organic layer is Na_2SO_4 dried, concentrated, and chromatographed ($MeCl_2$ to 5% EtOAc/$MeCl_2$) to give the title compound as a glassy solid (100 mg, 55%).

NMR

High Res. ES-MS: 480.2799; calc. for $C_{26}H_{38}O_5S+(NH_4)$: 480.2784

Examples 2 & 3

Preparation of enantiomers of isomers of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(methanesulfonyloxy)-3-methylphenyl]pentane.



A racemate mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(methanesulfonyloxy)-3-methylphenyl]pentane is chromatographed on (Chiralpak AD) to give isomer 1 (Example 2) of the title compound as an oil (22 mg, 36%) and isomer 2 (Example 3) of the title compound as an oil (20 mg, 34%).

Isomer 1

rt: 5.97 m (40% IPA/heptane)

NMR equivalent to Example 1.

High Res. ES-MS: 480.2765; calc. for $C_{26}H_{38}O_5S+(NH_4)$: 480.2784

Isomer 2

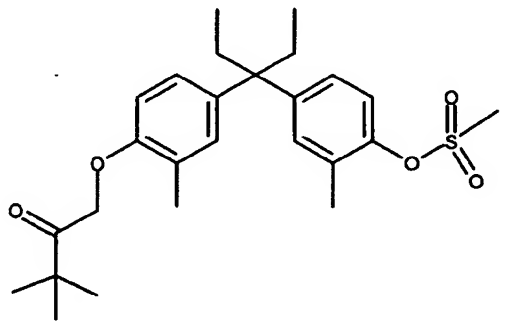
rt: 8.20 m (40% IPA/heptane)

NMR equivalent to Example 1.

High Res. ES-MS: 480.2773; calc. for $C_{26}H_{38}O_5S+(NH_4)$: 480.2784

Example 4

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(methanesulfonyloxy)-3-methylphenyl]pentane.



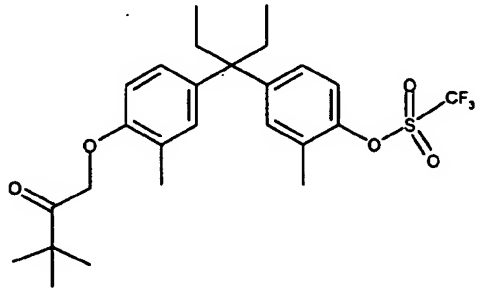
Using a procedure analogous to Example 1D, 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(hydroxy)-3-methylphenyl]pentane (Example 1B) gives the title compound (1.68 g, 61%).

NMR

FAB-MS: 460.4(M+).

Example 5

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(trifluoromethanesulfonyloxy)-3-methylphenyl]pentane.



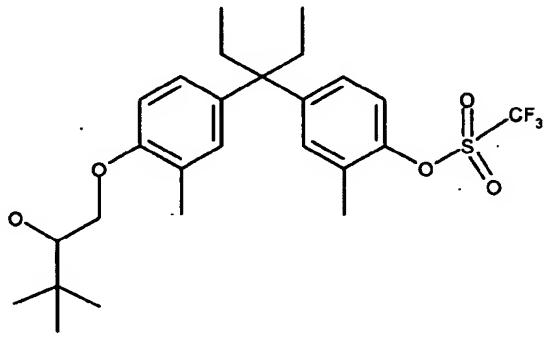
To a mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-hydroxy-3-methylphenyl]pentane (20 g, 52 mmol) and pyridine (30 ml) at 0 °C is added triflic anhydride (9.7 ml, 57 mmol). The reaction is warmed to RT and stirred overnight. The mixture is partitioned between Et_2O/1N HCl. The organic layer is washed with brine, Na_2SO_4 dried, concentrated, and chromatographed (hex to 10% EtOAc/hex) to give the title compound as an oil (26.3 g, 98%).

NMR

ES-MS: 532.5 (M+NH4).

Example 6

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(trifluoromethanesulfonyloxy)-3-methylphenyl]pentane.



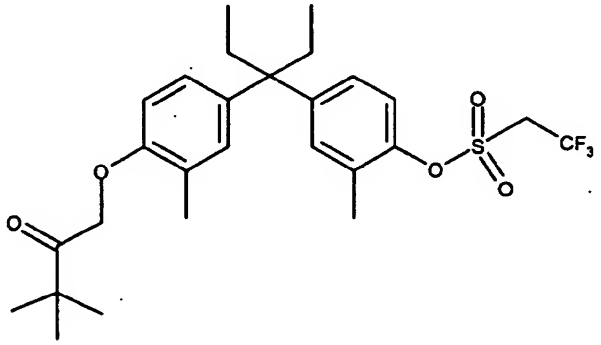
To a 0 °C mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(trifluoromethanesulfonyloxy)-3-methylphenyl]pentane (25.5 g, 49.5 mmol) and MeOH (200 ml) is added $NaBH_4$ (2.63 g, 69.3 mmol) in portions. The reaction is warmed to RT, stirred overnight, and concentrated. The mixture is partitioned between Et_2O/1N HCl. The organic layer is washed with water, Na_2SO_4 dried, and concentrated to give the title compound as an oil (26 g, quant).

NMR

High Res. EI-MS, m/e: 516.2171; calc. for $C_{26}H_{35}F_3O_5S$: 516.2157

Example 7

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(trifluoromethanesulfonyloxy)-3-methylphenyl]pentane.



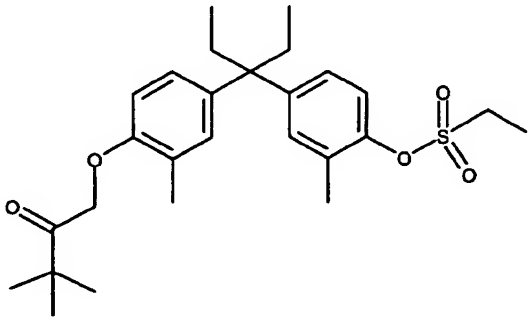
Using a procedure analogous to Example 1D, 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(hydroxy)-3-methylphenyl]pentane gives the title compound (290 mg, 21%).

NMR

High Res. ES-MS: 551.2048; calc. for $C_{27}H_{35}F_3O_5S$+(Na): 551.2055

Example 8

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(ethanesulfonyloxy)-3-methylphenyl]pentane.



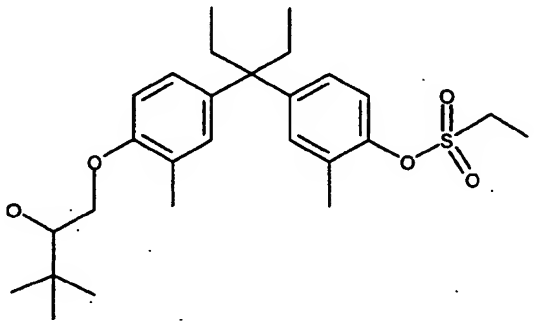
Using a procedure analogous to Example 1D, 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(hydroxy)-3-methylphenyl]pentane gives the title compound (1.0 g, 81%).

NMR

High Res. ES-MS: 497.2334; calc. for $C_{27}H_{38}O_5S$+Na: 497.2338.

Example 9

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(ethanesulfonyloxy)-3-methylphenyl]pentane.



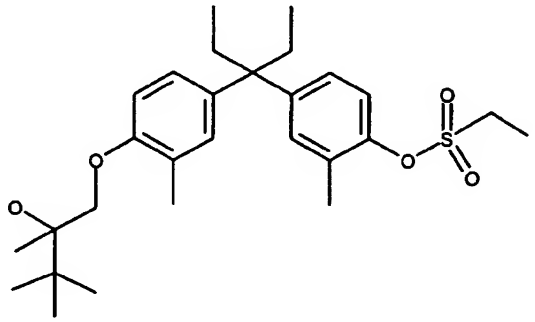
Using a procedure analogous to Example 1C, 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(hydroxy)-3-methylphenyl]pentane gives the title compound (550 mg, quant).

NMR

High Res. ES-MS: 499.2508; calc. for $C_{27}H_{40}O_5S$+Na: 499.2494.

Example 10

Preparation of 3'-[4-(2-hydroxy-2-methyl-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(ethanesulfonyloxy)-3-methylphenyl]pentane.

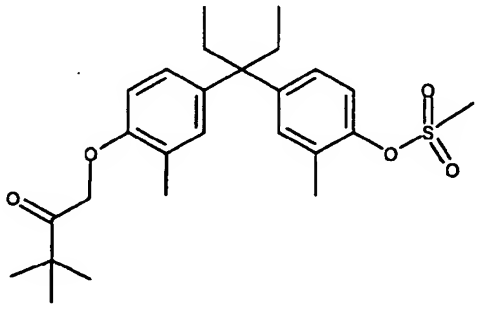


To a 0 C mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(ethanesulfonyloxy)-3-methylphenyl]pentane (200 mg, 0.42 mmol) in THF (1 ml) is added 3 M MeMgBr/THF (150 ul, 0.46 mmol), warmed to RT, and stirred overnight. The reaction is diluted with Et_2O, washed with 1 N HCl, water, brine, Na_2SO_4 dried, and chromatographed ($CHCl_3$ to 10% EtOAc/$CHCl_3$) to give the title compound (150 mg, 75%).

ES-MS: 489.1 (M-1).

Example 11

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(methanesulfonyloxy)-3-methylphenyl]pentane.



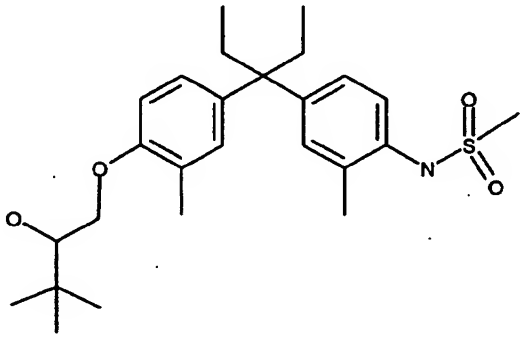
Using a procedure analogous to Example 1D, 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(hydroxy)-3-methylphenyl]pentane gives the title compound (1.68 g, 61%).

NMR

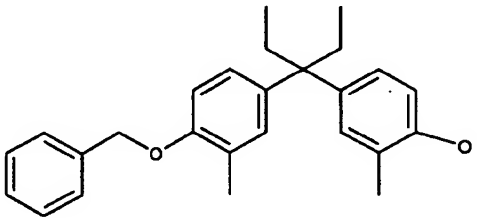
FAB-MS: 460.4 (M+).

Example 12

Preparation of 3'-[4-(2-hydroxy-2-methyl-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(methanesulfonylamino)-3-methylphenyl]pentane.

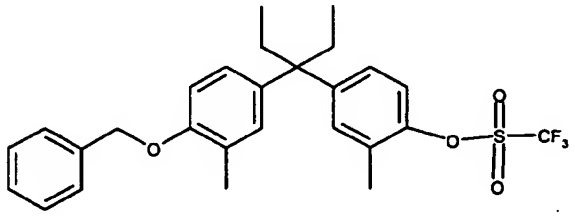


A. 3'-[4-(2-benzyloxy)-3-methylphenyl]-3'-[4-hydroxy-3-methylphenyl]pentane.



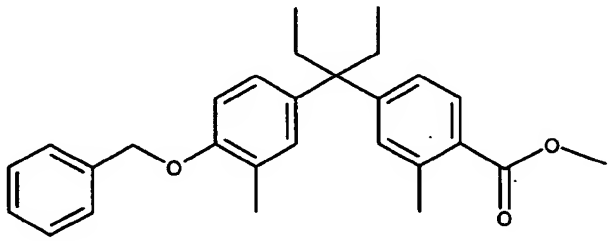
To a mixture of 3'-[4-(2-hydroxy)-3-methylphenyl]-3'-[4-hydroxy-3-methylphenyl]pentane (70 g, 246 mmol)/DMF (800 ml) is added 60% disp NaH (9.9 g, 246 mmol). After stirring for 90 m, benzyl bromide (4.2 ml, 35.2 mmol) is added dropwise. The reaction is stirred for 18 h and concentrated (vacuum at 50 C). The residue is added Et_2O/1 N HCl and partitioned. The organic layer is washed with water (2X), Na_2SO_4 dried, and concentrated. The residue is chromatographed (Hex to 20% EtOAc/Hex) to give the title compound (44 g, 48%, Rf=0.15; 10% EtAOc/Hex).

B. 3'-[4-(2-benzyloxy)-3-methylphenyl]-3'-[4-trifluoromethylsulfonyloxy-3-methylphenyl]pentane.



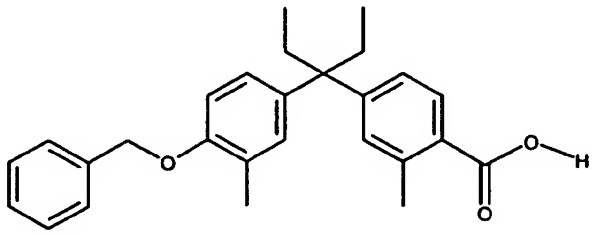
Using a procedure analogous to Example 5, 3'-[4-(2-benzyloxy)-3-methylphenyl]-3'-[4-hydroxy-3-methylphenyl]pentane gives the title compound (27 g, 95%). NMR

C. 3'-[4-(Benzyloxy)-3-methylphenyl]-3'-[4-(methoxycarbonyl)-3-methylphenyl]pentane.



A mixture of 3'-[4-(2-benzyloxy)-3-methylphenyl]-3'-[4-trifluoromethylsulfonyloxy-3-methylphenyl]pentane (35.5 g, 70 mmol), $Pd(OAc)_2$ (1.6 g, 7.0 mmol), DPPF (7.8 g, 14.0 mmol), MeOH (30 ml, 700 mmol), Et_3N (30 ml, 210 mmol), and DMF (133 ml) is pressurized with carbon monoxide (1000 psi) and heated to 110 °C for 48 h. After cooling, the reaction is filtered through diatomaceous earth with EtOAc wash. The filtrate is diluted with Et_2O, washed with 1N HCl, and filtered through diatomaceous earth. The filtrate is washed with water, Na_2SO_4 dried, concentrated, and chromatographed (Hex to 10% EtOAc/Hex) to give the title compound (26 g, 89%).

D. 3'-[4-(Benzyloxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane.

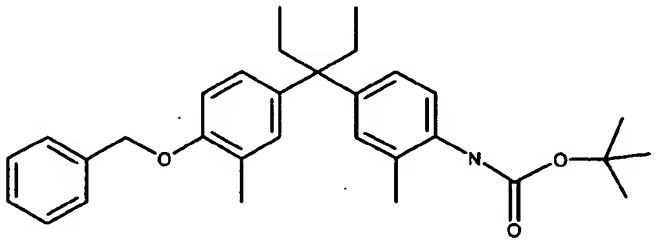


A mixture of 3'-[4-benzyloxy-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane (26 g, 62 mmol), EtOH (200 ml), water (100 ml) is added KOH (17 g, 300 mmol) and heated to 65 °C for 24 h. The reaction is concentrated and the residue was partitioned between Et_2O and 1N HCl. The organic layer is washed with water, Na_2SO_4 dried, concentrated, and chromatographed ($CHCl_3$ to 5% MeOH/$CHCl_3$) to give the title compound (23 g, 92%).

NMR

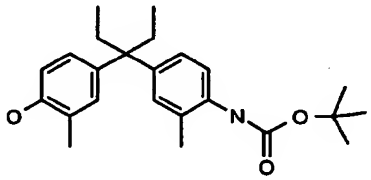
High Res. ES-MS (negative ion): 401.2099; calc. for $C_{27}H_{30}O_3$-H: 401.2117.

E. 3'-[4-(Benzyloxy)-3-methylphenyl]-3'-[4-(t-butoxycarbonylamino)-3-methylphenyl]pentane.



To a 0 C mixture of 3'-[4-(benzyloxy)-3-methylphenyl]-3'-[4-(carboxy)-3-methylphenyl]pentane (3.2 g, 7.9 mmol), Et3N (1.2 ml, 8.3 mmol), and CH_2Cl_2 (15 ml) is added $(PhO)_2PO(N_3)$ (1.8 ml, 8.2 mmol) and stirred for 1 h. The reaction is concentrated to a small volume. This concentrate is added to a 90 C solution of t-BuOH and heated with an open stream of nitrogen for 1.75 h. The reaction is cooled to RT, dissolved in a minimal of 1:1 CH_2Cl_2:10% EtOAc/Hex, and chromatographed (10% EtOAc/Hex) to give the title compound as a white glassy solid (2.6 g, 69%).

F. 3'-[4-(Hydroxy)-3-methylphenyl]-3'-[4-(t-butoxycarbonylamino)-3-methylphenyl]pentane.

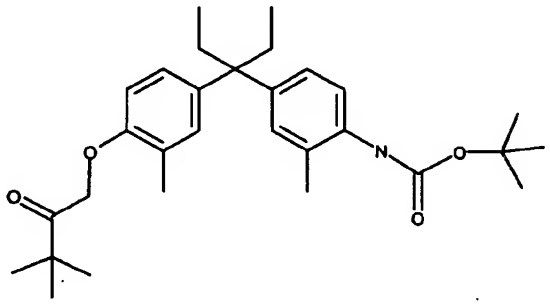


A mixture of 3'-[4-(benzyloxy)-3-methylphenyl]-3'-[4-(t-butoxycarbonylamino)-3-methylphenyl]pentane (2.45 g, 5.2 mmol), 10% Pd-C (250 mg), and EtOH (15 ml) is hydrogenated at 1 atmospheric pressure for 48 h. the reaction is filtered through diatomaceous earth with CH_2Cl_2 washes. The filtrate is concentrated and chromatograpghed (CH_2Cl_2 to 5% EtOAc/CH_2Cl_2) to give the title compound as a white glassy solid (2.0 g, quant).

NMR

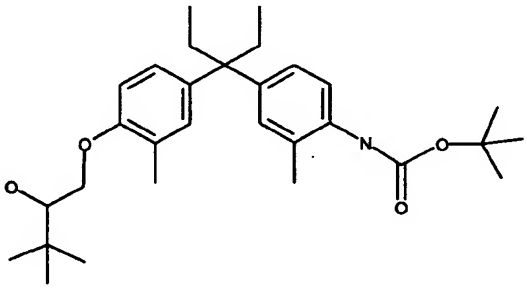
ES-MS: 384.2 (M+H).

G. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(t-butoxycarbonylamino)-3-methylphenyl]pentane.



Using a procedure analogous to Example 1B , 3'-[4-(hydroxy)-3-methylphenyl]-3'-[4-(t-butoxycarbonylamino)-3-methylphenyl]pentane gives the compound as a white glassy solid (2.3 g, 96%).

H. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(t-butoxycarbonylamino)-3-methylphenyl]pentane.

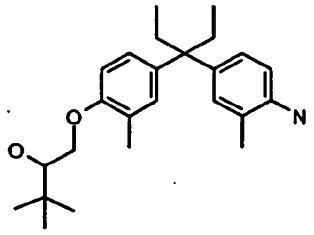


Using a procedure analogous to Example 1C, 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(t-butoxycarbonylamino)-3-methylphenyl]pentane gives the title compound as a white glassy solid (2.1 g, quant).

NMR

High Res. ES-MS: 501.3693; calc. for $C_{30}H_{45}NO_4$+(NH_4): 501.3692.

I. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-amino-3-methylphenyl]pentane.



To a mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(t-butoxycarbonylamino)-3-methylphenyl]pentane (2.2 g, 4.5 mmol), anisole (9.9 ml, 90.9 mmol), and CH_2Cl_2 (5 ml) is added TFA (7.0 ml, 90.9 mmol). The reaction is stirred for 2 h, concentrated, and partitioned between EtOAc/satd Na_2CO_3. The organic layer is washed with water, Na_2SO_4 dried, concentrated, and chromatographed (50% $CHCl_3$/Hex to $CHCl_3$) to give the title compound (250 mg, 92%).

NMR

High Res. ES-MS: 384.2915; calc. for $C_{25}H_{38}NO_2$: 384.2903.

J. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(methanesulfonylamino)-3-methylphenyl]pentane.

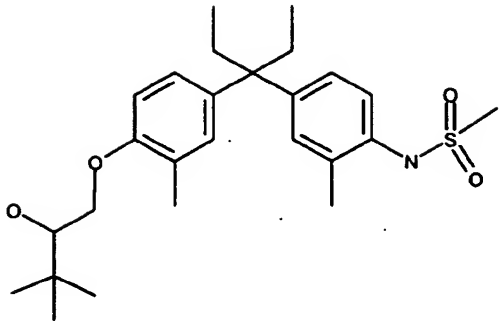
Using a procedure analogous to Example 5, 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(amino)-3-methylphenyl]pentane gives the title compound as a glassy white solid (240 mg, 80%).

NMR

High Res. FAB-MS: 461.2613; calc. for $C_{26}H_{39}NO_4S$: 461.2600.

Example 13 & 14

Preparation of enantiomers of 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(methanesulfonylamino)-3-methylphenyl]pentane.



A racemic mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(methanesulfonylamino)-3-methylphenyl]pentane is chromatographed (Chiralpak AD) to give enantiomer 1 (Example 13) of the title compound (82 mg, 41%) and enantiomer 2 (Example 14) of the title compound (73 mg, 37%).

Enantiomer 1

rt: 5.43 m (40% IPA/Hept); 225 nm.

NMR equivalent to Example 12.

High Res. ES-MS: 479.2966; calc. for $C_{26}H_{39}NO_4S+(NH_4)$: 479.2944

Enantiomer 2

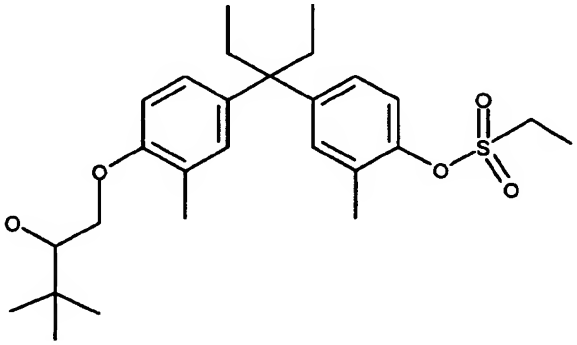
rt: 7.14 m (40% IPA/Hept); 225 nm.

NMR equivalent to Example 12.

High Res. ES-MS: 479.2932; calc. for $C_{26}H_{39}NO_4S+(NH_4)$: 479.2944

Example 15 & 16

Preparation of enantiomers of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(ethanesulfonyloxy)-3-methylphenyl]pentane.



A racemic mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(ethanesulfonyloxy)-3-methylphenyl]pentane is chromatographed on (Chiralpak AD) to give enantiomer 1 (Example 15) of the title compound (209 mg, quant) and enantiomer 2 (Example 16) of the title compound (199 mg, quant).

Enantiomer 1, Example 15

rt: 7.8 m (20% IPA/Hept); 220 nm.

NMR equivalent to Example 9.

High Res. ES-MS: 494.2943; calc. for $C_{27}H_{40}O_5S+(NH_4)$: 494.2940

Enantiomer 2, Example 16

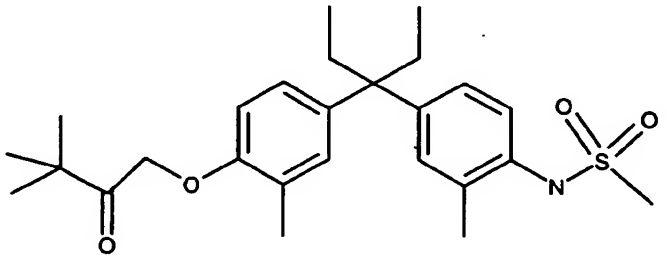
rt: 11.0 m (20% IPA/Hept); 220 nm.

NMR equivalent to Example 9.

High Res. ES-MS: 494.2960; calc. for $C_{27}H_{40}O_5S+(NH_4)$: 494.2940

Example 17

Preparation of N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-methanesulfonamide.



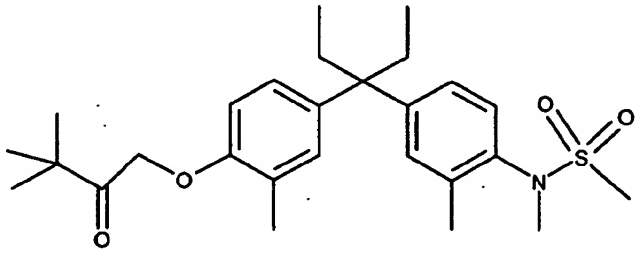
To a 0 °C mixture of 1-{4-[1-(4-amino-3-methyl-phenyl)-1-ethyl-propyl]-2-methyl-phenoxy}-3,3-dimethyl-butan-2-one (763 mg, 2 mmol), triethylamine (0.42 mL, 3 mmol) and CH_2Cl_2 (7 mL) is added methanesulfonyl chloride (0.155 mL, 2 mmol). The reaction is warmed to RT and stirred for 3 h. The reaction is diluted with CH_2Cl_2 dichloromethane and washed with 0.2 N HCl. The organic phase is Na2SO4 dried, concentrated, and chromatogrpahed (0% to 25% EtOAc/Hex) to give the title compound (800 mg, 87%).

^{1}H NMR ($CDCl_3$) δ 7.29 (d, 1H, J = 8.3 Hz), 7.03 (d, 1H, J = 8.3 Hz), 6.99 (s, 1H), 6.89 (s, 1H), 6.88 (d, 1H, J = 8.3 Hz), 6.49 (d, 1H, J = 8.3 Hz), 6.02 (s, 1H), 4.84 (s, 2H), 3.01 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.03 (q, 4H), 1.25 (s, 9H), 0.58 (t, 6H).

HRMS: calcd. for C26H41N2O4S (M+18), 477.2787, found, 477.2801.

Example 18

Preparation of N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-N-methyl-methanesulfonamide



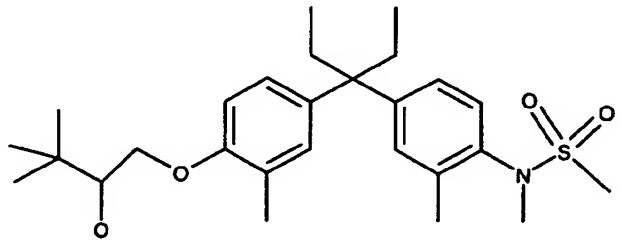
To a mixture of N-(4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-methanesulfonamide (230 mg, 0.5 mmol), triphenyl phosphine (197 mg, 0.75 mmol), MeOH (0.03 mL, 0.75 mmol), and THF (10 mL) is added diethylazodicarboxylate (0.12 mL, 0.75 mmol) and stirred overnight. The reaction is concentrated and chromatographed (0% to 25% EtOAc/Hex) to give the title compound (180 mg, 76%).

^{1}H NMR ($CDCl_3$) δ 7.09 (s, 1H), 7.07 (d, 1H, J = 8.4 Hz), 6.97 (dd, 1H, J = 2.2, 8.4 Hz), 6.92 (s, 1H), 6.88 (dd, 1H, J = 2.2, 8.4 Hz), 6.49 (d, 1H, J = 8.4 Hz), 4.85 (s, 2H), 3.21 (s, 3H), 2.95 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H), 2.03 (q, 4H), 1.25 (s, 9H), 0.58 (t, 6H).

HRMS: calcd. for C27H43N2O4S (M+18), 491.2944, found, 491.2939.

Example 19

Preparation of N-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-phenyl)-N-methyl-methanesulfonamide



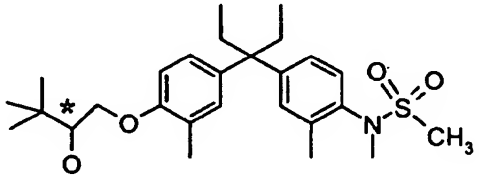
To a 0 °C mixture of N-(4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-N-methyl-methanesulfonamide (100 mg, 0.21 mmol), MeOH (5 mL), and THF (10 mL) is added $NaBH_4$ (12 mg, 0.32 mmol). The reaction is warmed to RT and stirred for 5 h and concentrated. The residue is partitioned between EtOAc and 0.2 N HCl. The organic phase is Na_2SO_4 dried, concentrated, and chromatographed (0% to 25 % EtOAc/Hex) to give the title compound (60 mg, 60%).

^{1}H NMR ($CDCl_3$) δ 7.09 (s, 1H), 7.08 (d, 1H, J = 8.3 Hz), 6.97 (dd, 1H, J = 2.0, 8.3 Hz), 6.93 (dd, 1H, J = 2.0, 8.3 Hz), 6.92 (s, 1H), 6.71 (d, 1H, J = 8.3 Hz), 4.10 (dd, 1H, J = 2.7, 8.7 Hz), 3.87 (dd, 1H, J = 8.7, 8.8 Hz), 3.72 (dd, 1H, J = 2.4, 8.8 Hz), 3.22 (s, 3H), 2.96 (s, 3H), 2.36 (s, 3H), 2.20 (s, 3H), 2.05 (q, 4H), 1.03 (s, 9H), 0.62 (t, 6H).

HRMS: calcd. for C27H41NO4NaS (M+23), 498.2654, found, 498.2657.

Example 20 and Example 21

Preparation of enantiomers of N-(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-phenyl)-N-methyl-methanesulfonamide



A racemic mixture of N-(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-phenyl)-N-methyl-methanesulfonamide (48 mg) is chromatographed (Chiralpak AD column) to give enantiomer 1, Example 20 (13 mg, 27%) and enantiomer 2, Example 21 (12 mg, 25%).

HPLC: Chiralpak AD (4.6 x 150 mm); 60% heptane, 40% 2-propanol; flow rate: 1.0 ml/m; UV: 225 nm

Enantiomer 1, Example 20: rt = 4.98 m;

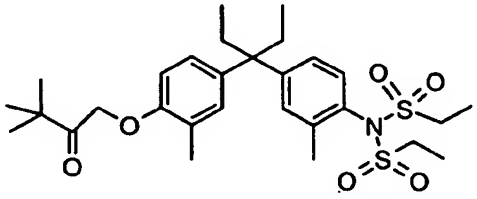
^{1}H NMR ($CDCl_3$): equivalent to Example 19

Enantiomer 2, Example 21: rt = 5.97 m.

^{1}H NMR ($CDCl_3$): equivalent to Example 19

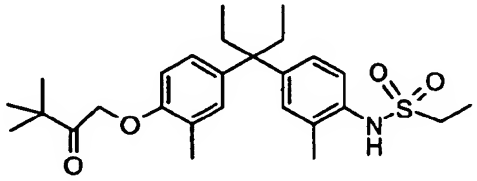
Example 22 and Example 23

Preparation of N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-N, N-bis-ethanesulfonamide



and

and N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-ethanesulfonamide



Using a procedure analogous to Example 17, 1-{4-[1-(4-amino-3-methyl-phenyl)-1-ethyl-propyl]-2-methyl-phenoxy}-3,3-dimethyl-butan-2-one (229 mg, 0.6 mmol), ethanesulfonyl chloride (0.080 mL, 0.9 mmol) gives N-(4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-N, N-bis-ethanesulfonamide (Example 22) (120 mg, 35%), and N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-ethanesulfonamide (Example 23) (130 mg, 46%),.

for Example 22

^{1}H NMR ($CDCl_3$) δ 7.15 (d, 1H, J = 8.3 Hz), 7.10 (s, 1H), 7.01 (d, 1H, J = 8.8 Hz), 6.94 (s, 1H), 6.86 (d, 1H, J = 8.8 Hz), 6.49 (d, 1H, J = 8.3 Hz), 4.85 (s, 2H), 3.55, 3.72 (m, 4H), 2.40 (s, 3H), 2.27 (s, 3H), 2.04 (q, 4H), 1.54 (m, 6H), 1.27 (s, 9H), 0.59 (t, 6H); LC-MS: 583 (M+18).

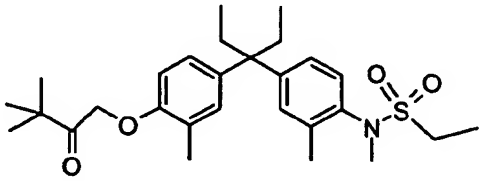
for Example 23

^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H, J = 8.3 Hz), 7.01 (dd, 1H, J = 2.0, 8.3 Hz), 6.97 (s, 1H), 6.89 (s, 1H), 6.86 (d, 1H, J = 8.3 Hz), 6.49 (d, 1H, J = 8.3 Hz), 5.97 (s, 1H), 4.85 (s, 2H), 3.16 (q, 2H), 2.27 (s, 3H), 2.25 (s, 3H), 2.04 (q, 4H), 1.41 (t, 3H), 1.27 (s, 9H), 0.59 (t, 6H).

LC-MS: 491 (M+18).

Example 24

Preparation of N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-N-methyl-ethanesulfonamide.



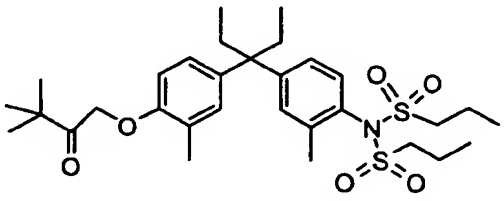
The title compound is prepared from N-(4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-ethanesulfonamide and methanol using a procedure analogous to Example 18 (78%).

^{1}H NMR ($CDCl_3$) δ 7.09 (d, 1H, J = 8.4 Hz), 7.08 (s, 1H), 6.96 (dd, 1H, J = 2.0, 8.4 Hz), 6.92 (d, 1H, J = 2.2 Hz), 6.88 (dd, 1H, J = 2.2, 8.4 Hz), 6.49 (d, 1H, J = 8.4 Hz), 4.85 (s, 2H), 3.22 (s, 3H), 3.12 (q, 2H), 2.35 (s, 3H), 2.25 (s, 3H), 2.03 (q, 4H), 1.43 (t, 3H), 1.25 (s, 9H), 0.60 (t, 6H).

HRMS: calcd. for C28H41NO4NaS (M+23), 510.2654, found, 510.2666.

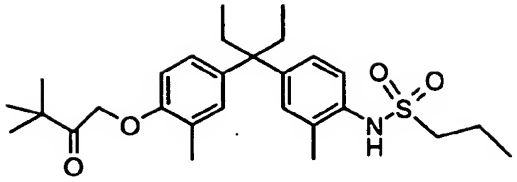
Example 25 and Example 26

N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-N,N-bis-1-propanesulfonamide



and

N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-1-propanesulfonamide



Using a procedure analogous to Example 22 and Example 23, 1-{4-[1-(4-amino-3-methyl-phenyl)-1-ethyl-propyl]-2-methyl-phenoxy}-3,3-dimethyl-butan-2-one and 1-propane-sulfonyl chloride give the title compounds Example 25 (34%) and Example 26 (42%).

for Example 25:

^{1}H NMR ($CDCl_3$) δ 7.13 (d, 1H, J = 8.3 Hz), 7.10 (s, 1H), 7.01 (d, 1H, J = 8.3 Hz), 6.94 (s, 1H), 6.87 (d, 1H, J = 8.8 Hz), 6.49 (d, 1H, J = 8.8 Hz), 4.85 (s, 2H), 3.63 (m, 2H), 3.50 (m, 2H), 2.39 (s, 3H), 2.25 (s, 3H), 1.92, 2.06 (m, 8H), 1.26 (s, 9H), 1.09 (t, 6H), 0.59 (t, 6H);

HRMS: Calcd. for $C_{31}H_{47}NO_6NaS_2$ (M+23), 616.2743, found, 616.2769;

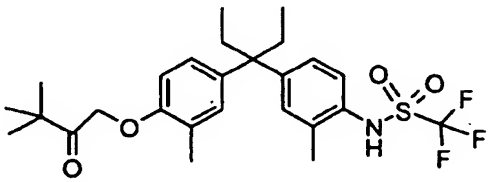
for Example 26:

^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H, J = 8.8 Hz), 7.00 (dd, 1H, J = 2.4, 8.3 Hz), 6.97 (s, 1H), 6.89 (s, 1H), 6.87 (d, 1H, J = 8.8 Hz), 6.49 (d, 1H, J = 8.3 Hz), 6.00 (s, 1H), 4.84 (s, 2H), 3.09 (q, 2H), 2.25 (s, 3H), 2.23 (s, 3H), 2.02 (q, 4H), 1.87 (q, 2H), 1.25 (s, 9H), 1.04 (t, 3H), 0.58 (t, 6H);

HRMS: Calcd. for $C_{28}H_{41}NO_4NaS$ (M+23), 510.2654, found, 510.2664.

Example 27

N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-trifluoromethanesulfonamide

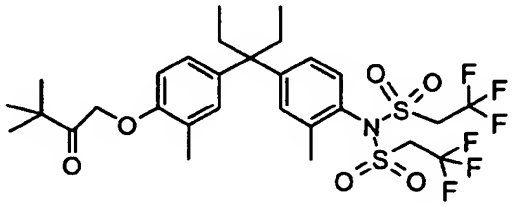


The title compound is prepared from 1-{4-[1-(4-amino-3-methyl-phenyl)-1-ethyl-propyl]-2-methyl-phenoxy}-3,3-dimethyl-butan-2-one and trifluoromethane sulfonyl chloride using a procedure analogoues to Example 17 (45%).

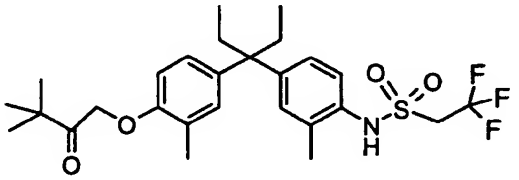
^{1}H NMR ($CDCl_3$) δ 6.94 (s, 1H), 6.92 (d, 1H, J = 8.3 Hz), 6.83 (s, 1H), 6.81 (d, 1H, J = 8.8 Hz), 6.58 (d, 1H, J = 8.8 Hz), 6.49 (d, 1H, J = 8.3 Hz), 4.84 (s, 2H), 2.25 (s, 3H), 2.13 (s, 3H), 2.01 (q, 4H), 1.27 (s, 9H), 0.59 (t, 6H).

Example 28 and Example 29

Preparation of N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)- N,N-bis-2,2,2-trifluoro-ethanesulfonamide



N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2,2,2-trifluoro-ethanesulfonamide



Using a procedure analogous to Example 22 and Example 23, 1-{4-[1-(4-amino-3-methyl-phenyl)-1-ethyl-propyl]-2-methyl-phenoxy}-3,3-dimethyl-butan-2-one and 1-propane-sulfonyl chloride give the title compounds Example 28 (49%) and Example 29 (25%).

for Example 28:

^{1}H NMR ($CDCl_3$) δ 7.16 (s, 1H), 7.08 (s, 2H), 6.93 (s, 1H), 6.86 (d, 1H, J = 8.3 Hz), 6.49 (d, 1H, J = 8.8 Hz), 4.86 (s, 2H), 4.49 (m, 2H), 4.34 (m, 2H), 2.38 (s, 3H), 2.27 (s, 3H), 2.05 (q, 4H), 1.27 (s, 9H), 0.61 (t, 6H);

HRMS: Calcd. for C29H41N2O6F6S2 (M+18), 691.2310, found, 691.2337;

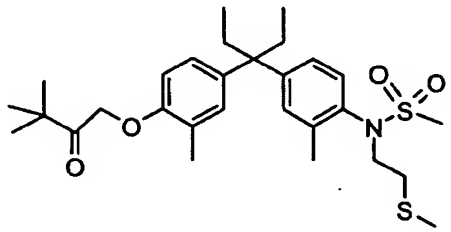
for Example 29:

^{1}H NMR ($CDCl_3$) δ 7.26 (d, 1H, J = 8.8 Hz), 7.03 (m, 2H), 6.89 (s, 1H), 6.87 (d, 1H, J = 8.3 Hz), 6.49 (d, 1H, J = 8.8 Hz), 6.02 (s, 1H), 4.85 (s, 2H), 3.87 (m, 2H), 2.28 (s, 3H), 2.24 (s, 3H), 2.03 (q, 4H), 1.25 (s, 9H), 0.59 (t, 6H).

HRMS: calcd. for C27H40N2O4F3S (M+18), 545.2661, found, 545.2685.

Example 30

N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-N-(2-methylsulfanyl-ethyl)-methanesulfonamide



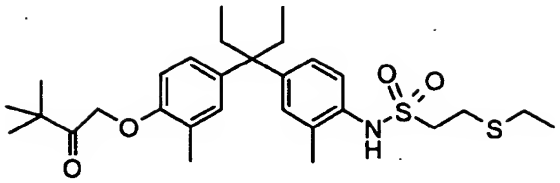
The title compound is prepared from N-(4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-methanesulfonamide and 2-methylsulfanyl-ethanol using a procedure analogous to Example 18 (58%).

^{1}H NMR ($CDCl_3$) δ 7.10 (d, 1H, J = 2.0 Hz), 7.08 (d, 1H, J = 8.4 Hz), 6.97 (dd, 1H, J = 2.0, 8.4 Hz), 6.92 (d, 1H, J = 2.0 Hz), 6.88 (dd, 1H, J = 2.4, 8.8 Hz), 6.49 (d, 1H, J = 8.8 Hz), 4.85 (s, 2H), 3.75 (m, 2H), 2.99 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H), 2.10 (m, 2H), 2.02 (q, 4H), 1.73 (s, 3H), 1.25 (s, 9H), 0.59 (t, 6H).

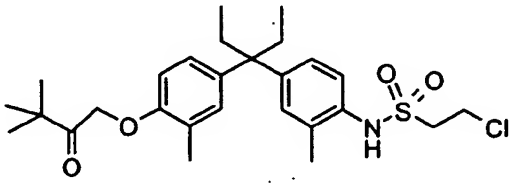
HRMS: calcd. for C29H47N2O4S2 (M+18), 551.2977, found, 551.2984.

Example 31

N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2-ethylsulfanyl-ethanesulfonamide



A. N-(4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2-chloro-ethanesulfonamide



Using a procedure analogous to Example 17, 1-{4-[1-(4-amino-3-methyl-phenyl)-1-ethyl-propyl]-2-methyl-phenoxy}-3,3-dimethyl-butan-2-one (382 mg, 1 mmol), 2-chloro-ethanesulfonyl chloride (0.1 mL, 1 mmol) and triethylamine (0.14 mL, 1 mmol) give the title compound as a oil (500 mg, quant.)

ESMS$^-$: 470 (M-HCl);

B. N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2-ethylsulfanyl-ethanesulfonamide

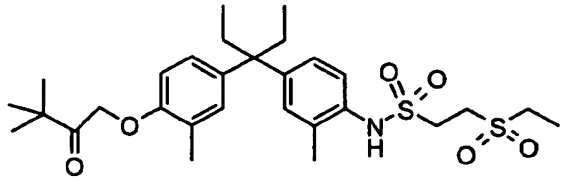
A 0 °C solution of ethanethiol (0.1 mL, 1.35 mmol) in THF (5 mL) is treated with NaH (81 mg, 2 mmol, 60% in mineral oil) and stirred for 10 m. The mixture is added a solution of N-(4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2-chloro-ethanesulfonamide (500 mg, 1mmol) in THF (10 mL), warmed to RT, and stirred overnight. The reaction is concentrated, dissolved in CH_2Cl_2, and washed with 0.2 N HCl. The organic layer is concentrated and chromatographed (0%-20% EtOA/Hex) to give the title compound (270 mg, 51%).

^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H, J = 8.3 Hz), 7.02 (d, 1H, J = 8.3 Hz), 6.98 (s, 1H), 6.87, 6.89 (m, 2H), 6.49 (d, 1H, J = 8.8 Hz), 6.27 (s, 1H), 4.85 (s, 2H), 3.36 (m, 2H), 3.30 (m, 2H), 2.51 (q, 2H), 2.28 (s, 3H), 2.25 (s, 3H), 2.03 (q, 4H), 1.27 (s, 9H), 1.22 (t, 3H), 0.60 (t, 6H);

HRMS: Calcd. for C29H44NO4S2 (M+1), 534.2712, found, 534.2736.

Example 32

N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2-ethanesulfonyl-ethanesulfonamide



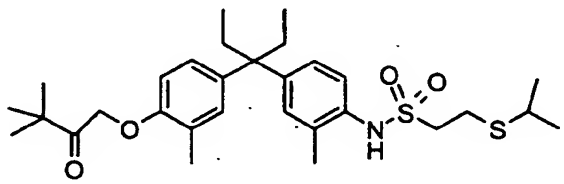
To a solution of N-(4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2-ethylsulfanyl-ethanesulfonamide (220 mg, 0.41 mmol) in dichloromethane (10 mL) is added m-chloroperbenzoic acid (427 mg, 1.24 mmol, 50%) at RT. After stirring for 3 h, the reaction is concentrated and chromatographed (0%-33% EtOAc/Hex) to give the title compound (190 mg, 81%).

^{1}H NMR ($CDCl_3$) δ 7.27 (d, 1H, J = 8.3 Hz), 7.03 (d, 1H, J = 8.3 Hz), 7.02 (s, 1H), 6.86, 6.90 (m, 2H), 6.50 (d, 1H, J = 8.3 Hz), 6.19 (s, 1H), 4.85 (s, 2H), 3.60 (m, 2H), 3.44 (m, 2H), 3.08 (q, 2H), 2.30 (s, 3H), 2.25 (s, 3H), 2.03 (q, 4H), 1.45 (t, 3H), 1.27 (s, 9H), 0.60 (t, 6H);

HRMS: Calcd. for C29H43NO6NaS2 (M+23), 588.2430, found, 588.2406.

Example 33

N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2-isopropylsulfanyl-ethanesulfonamide



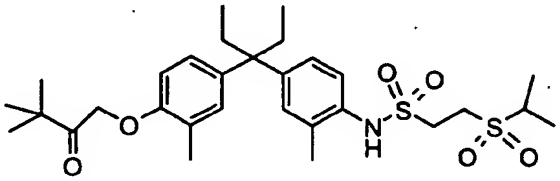
Using a procedure analogous to Example 31B, 4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2-chloro-ethanesulfonamide (Example 31A) and propane-2-thiol give the title compound (44%).

^{1}H NMR ($CDCl_3$) δ 7.29 (d, 1H, J = 8.3 Hz), 7.02 (d, 1H, J = 8.8 Hz), 6.98 (s, 1H), 6.89 (s, 1H), 6.88 (d, 1H, J = 8.3 Hz), 6.49 (d, 1H, J = 8.8 Hz), 6.09 (s, 1H), 4.85 (s, 2H), 3.35 (t, 2H), 2.92 (m, 3H), 2.27 (s, 3H), 2.25 (s, 3H), 2.03 (q, 4H), 1.27 (s, 9H), 1.23 (d, 6H), 0.60 (t, 6H);

HRMS: Calcd. for C30H45NO4NaS2 (M+23), 570.2688, found, 570.2680.

Example 34

N-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2-(propane-2-sulfonyl)-ethanesulfonamide



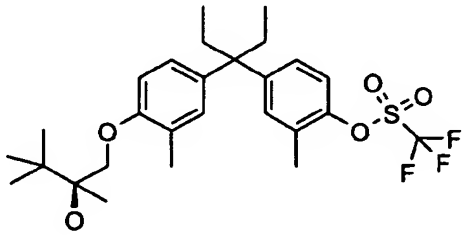
Using a procedure analogous to Example 32, 4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenyl)-2-(isopropylsulfanyl)ethanesulfonamide and m-chloroperbenzoic acid give the title compound (75%).

^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H, J = 8.4 Hz), 7.03 (d, 1H, J = 8.4 Hz), 7.01 (s, 1H), 6.90 (s, 1H), 6.87 (d, 1H, J = 8.4 Hz), 6.50 (d, 1H, J = 8.4 Hz), 6.24 (s, 1H), 4.84 (s, 2H), 3.59 (m, 2H), 3.39 (m, 2H), 3.16 (m, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 2.02 (q, 4H), 1.41 (d, 6H), 1.25 (s, 9H), 0.59 (t, 6H);

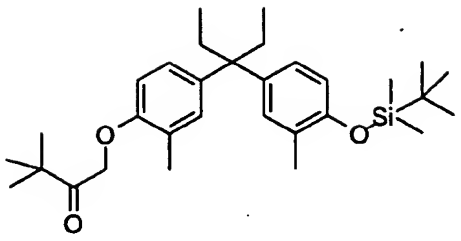
HRMS: Calcd. for $C_{30}H_{46}NO_6S_2$ (M+1), 580.2767, found, 580.2779.

Example 35

Preparation of trifluoro-methanesulfonic acid 4-{1-ethyl-1-[4-(2-hydroxy-2,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-phenyl ester.

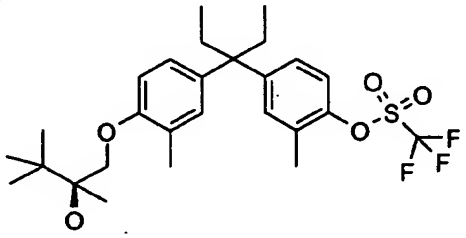


A. 1-(4-{1-[4-(tert-Butyl-dimethyl-silanyloxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-one.



Using a procedure analogous to Example 13A, 1-{4-[1-Ethyl-1-(4-hydroxy-3-methyl-phenyl)-propyl]-2-methyl-phenoxy}-3,3-dimethyl-butan-2-one (Example 1B) (4.91 g, 12.83 mmol) and TBSCl (1.93 g, 12.83 mmol) give the title compound (5.74 g, 11.57 mmol, 90%). ^{1}H NMR ($CDCl_3$), δ 0.21 (s, 6H), 0.60 (t, J = 7.5 Hz, 6H), 1.01(s, 9H), 1.26 (s, 9H), 2.01 (q, J = 7.5 Hz, 4H), 2.16 (s, 3H), 2.24 (s, 3H), 4.83 (s, 2H), 6.50 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 6.82 (dd, J = 8.4, 2.3 Hz, 1H), 6.87-6.93 (m, 3H). LC/MS (m/z): calcd for $C_{31}H_{52}NO_3Si$ $(M+NH_4)^+$: 514.8; found: 514.5.

B. Trifluoro-methanesulfonic acid 4-{1-ethyl-1-[4-(2-hydroxy-2,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-phenyl ester.

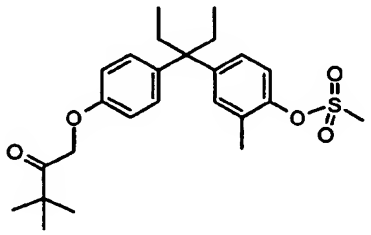


To a solution of 1-(4-{1-[4-(tert-Butyl-dimethyl-silanyloxy)-3-methyl-phenyl]-1-ethyl-propyl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-one (5.63 g, 11.40 mmol) in THF (100 mL) is treated with 3.0 M CH_3MgBr (5.7 mL, 17.24 mmol). The reaction is stirred for 1 h, quenched with satd NH_4Cl (50 mL) at 0 °C, diluted with EtOAc (100 mL), washed with 0.1 M HCl (2 x 50 mL), $MgSO_4$ dried, and concentrated. The resulting residue is dissolved in THF (50 mL), and reacted with 1.0 M TBAF (12.6 mL, 12.6 mmol) for 1h. The reaction is diluted with EtOAc (100 mL), washed with 0.1 M HCl (3 x 50 mL), brine (50 mL), $MgSO_4$ dried, and concentrated. The resulting residue is dissolved in CH_2Cl_2 (100 mL), cooled to 0 °C, treated with Et_3N (1.7 mL, 12.38 mmol) and Tf_2O

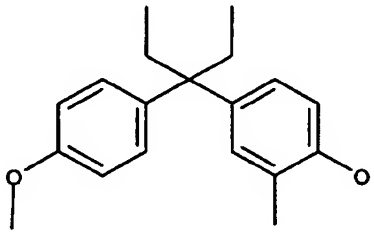
(1.9 mL, 11.35 mmol). After stirring 5 m, the reaction is washed with 0.1 M HCl (2 x 50 mL), $MgSO_4$ dried, concentrated, and chromatographed to give the title compound (5.30 g, 10.0 mmol, 87% for 3-steps). ^1H NMR ($CDCl_3$), δ 0.61 (t, J = 7.1 Hz, 6H), 1.05(s, 9H), 1.34 (s, 3H), 2.05(q, J = 7.1 Hz, 4H), 2.21 (s, 3H), 2.33 (s, 3H), 3.84 (d, J = 8.9 Hz, 1H), 4.01 (d, J = 8.9 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 2.2 Hz, 1H), 6.93 (dd, J = 8.8, 2.6 Hz, 1H), 7.02-7.11 (m, 3H). LC/MS (m/z): calcd for $C_{27}H_{41}NF_3O_5S$ (M $+NH_4)^+$: 548.7; found: 548.2.

Example 36

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-phenyl]-3'-[4-methylsulfonyloxy-3-methylphenyl]pentane.



A. 3'-(4-Methoxyphenyl)-3'-(4-hydroxy-3-methylphenyl)pentane.



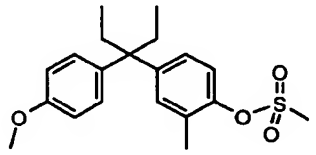
To a mixture of 3-(4-methoxyphenyl)-3-pentanol (ref. 1) (0.19 g, 1 mmol) and o-cresol (0.8 g, 7.4 mmol) is added BF3-ethereate (4 drops) and stirred for 16 h. The mixture is partitioned between diethylether and water, and the organic layer is Na_2SO_4 dried, and concentrated. The residue is vacuum dried (70-2 °C/0.04 mm) for 16 h to give the title compound (0.19 g, 67%).

H-NMR (400 mHz, CDCl3): 7.06 (2H, d, J = 8.8 Hz), 6.85 (2H, m), 6.77 (2H, d, 8.8 Hz), 6.64 (1H, d, J = 8.0 Hz), 4.75 (1H, s), 3.77 (3H, s), 2.18 (3H, s), 2.01 (4H, q, J = 7.4 Hz), 0.59 (6H, t, J = 7.4 Hz).

ES/MS: 283.2 (M+1).

Ref. 1: Collins, David J.; Jacobs, Howard A. Steric and stereoelectronic effects in the hydrogenolysis and Birch reduction of some hindered tertiary-benzylic carbinols. Australian Journal of Chemistry (1987), 40(12), 1989-2004.

B. 3'-(4-Methoxyphenyl)-3'-(4-methylsulfonyloxy-3-methylphenyl)pentane.

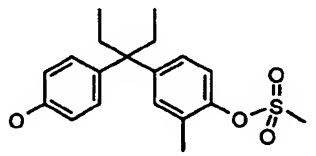


To a mixture of 3'-(4-methoxyphenyl)-3'-(4-hydroxy-3-methylphenyl)pentane (0.19 g, 0.67 mmol) and methanesulfonyl chloride (62 uL, 0.8 mmol) and of methylene chloride (10 mL) is added diisopropylethylamine (139 uL, 0.8 mmol). After stirring for 16 h, the reaction is quenched with saturated sodium bicarbonate. The organic layer is Na_2SO_4 dried, concentrated to give the title compound (0.19 g, 78%).

H-NMR (400 mHz, CDCl3): 7.12 (1H, d, J = 8.4 Hz), 7.03 (4H, m), 6.78 (2H, d, J = 8.8 Hz), 3.78 (3H, s), 3.16 (3H, s), 2.29 (3H, s), 2.03 (4H, q, J = 7.2 Hz), 0.59 (6H, t, J = 7.2 Hz).

ES/MS: 380.3 (M+NH4)

C. 3'-(4-Hydroxyphenyl)-3'-(4-methylsulfonyloxy-3-methylphenyl)pentane.



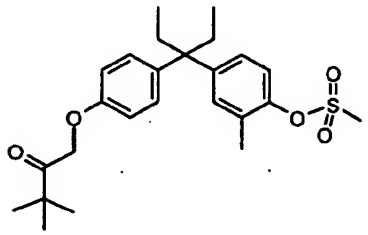
To a mixture of 3'-(4-methoxyphenyl)-3'-(4-methylsulfonyloxy-3-methylphenyl)pentane (0.19 g, 0.5 mmol) and methylene chloride (2 ml) is added 1.0 M boron tribromide (1.0 ml, 1.0 mmol). After stirring for 1 h, the mixture is quenched with

satd $NaHCO_3$. The organic phase is Na_2SO_4 dried and concentrated to give the title compound (0.17 g, 99%).

H-NMR (400 mHz, CDCl3): 7.06 (1H, d, J = 8.6 Hz), 7.01 (4H, m), 6.72 (2H, d, 8.4 Hz), 4.71 (1H, s), 3.15 (3H, s), 2.29 (3H, s), 2.02 (4H, q, J = 7.4 Hz), 0.59 (6H, t, J =7.4 Hz).

ES/MS: 366.3 (M+NH4)

D. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-phenyl]-3'-[4-methylsulfonyloxy-3-methylphenyl]pentane.



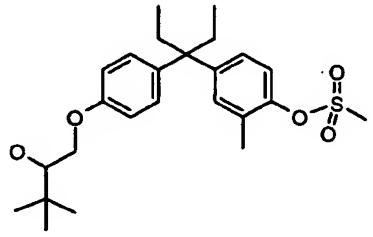
To a mixture of Hex washed NaH (15 mg 60% in mineral oil, 0.6 mmol) and DMF (2 mL) is added 3'-(4-hydroxyphenyl)-3'-(4-methylsulfonyloxy-3-methylphenyl)pentane (0.17g, 0.5 mmol) and 1-chloropinacolone (81 mg, 0.6 mmol). After stirring for 16 h, the reaction is quenched with satd $NaHCO_3$ and extracted with diethyl ether. The organic layer is washed with water, Na_2SO_4 dried, concentrated, and chromatographed (7.5% EtOAc/Hex to 12% EtOAc/Hex) to give the title compound (0.12 g, 55%).

H-NMR (300 mHz, DMSO-d6): δ 7.20 (1H, d, J = 8.2 Hz), 7.12 (1H, s), 7.04 (3H, m), 6.76 (2H, d, J = 8.2 Hz), 5.05 (2H, s), 3.41 (3H, s), 2.24 (3H, s), 2.04 (4H, q, J = 7.4 Hz), 1.15 (9H, s), 0.55 (6H, t, J = 7.4 Hz).

ES/MS: 464.3 (m+NH4).

Example 37

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-phenyl]-3'-[4-methylsulfonyloxy-3-methylphenyl]pentane.



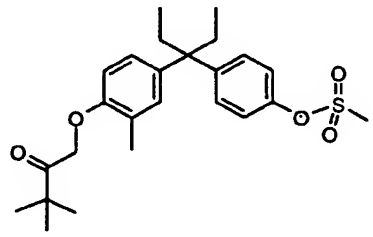
To a mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-phenyl]-3'-[4-methylsulfonyloxy-3-methylphenyl]pentane (84 mg, 0.19 mmol) and EtOH (2 ml) is added sodium borohydride (7 mg, 0.19 mmol). After stirring for 30 m, the mixture is quenched with satd $NaHCO_3$ and water and extracted with diethyl ether. The organic layer is Na_2SO_4 dried, concentrated, and chromatographed (7.5% EtOAc/Hex to 15% EtOAc/Hex) to give the title compound (59 mg, 69%).

H-NMR (400 mHz, CDCl3): δ 7.13 (1H, d, J = 8.4 Hz), 7.04 (4H, m), 6.80 (2H, d, J = 8.8 Hz), 4.09 (2H, d, J = 10.0 Hz), 3.84 (1H, t, J = 9.8 Hz), 3.67 (1H, d, J = 10 Hz), 3.16 (3H, s), 2.29 (3H, s), 2.03 (4H, q, J = 7.0 Hz), 0.99 (9H, s), 0.60 (6H, t, J = 7.0 Hz).

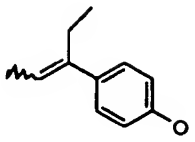
FAB/MS: 448.2 (m+).

Example 38

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methylsulfonyloxy-phenyl]pentane.



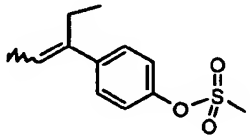
A. z/e-3-(4-Hydroxyphenyl)-3-pentene.



Using a procedure analogous to Example 36 C, 3-(4-methoxyphenyl)-3-pentanol (0.4 g, 2 mmol) and 1M boron tribromide (4 ml, 4 mmol) give the title compound (0.28 g, 86%).

H-NMR (400 mHz, CDCl3): 5.63 (0.6 H, q, J = 6.8 Hz), 5.48 (0.4 H, q, J = 6.8 Hz).

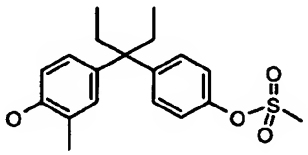
B. z/e-3'-(4-Methylsulfonyloxyphenyl)-3'-pentene.



Using a procedure analogous to Example 36 B, z/e-3-(4-hydroxyphenyl)-3-pentene (0.28 g, 1.7 mmol) gives the title compound (0.34 g, 84%).

H-NMR (400 mHz, CDCl3): 5.72 (0.6 H, q, J = 6.9 Hz), 5.54 (0.4 H, q, J = 6.9 Hz).

C. 3'-(4-Hydroxy-3-methylphenyl)-3'-(4-methylsulfonyloxy-phenyl)pentane.

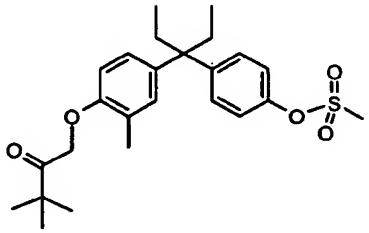


Using a procedure analogous to Example 36 A, z/e-3'-(4-methylsulfonyloxyphenyl)-3'-pentene (0.34 g, 1.4 mmol) gives the title compound (0.33 g, 68%).

H-NMR (400 mHz, CDCl3): 7.19 (2H, d, J = 8.0 Hz), 7.14 (2H, d, J = 8.0 Hz), 6.85 (1H, s), 6.83 (1H, d, J = 7.2 Hz), 6.64 (1H, d, J = 7.2 Hz), 4.58 (1H, m), 3.11 (3H, s), 2.19 (3H, s), 2.03 (4H, q, J = 7.4 Hz), 0.59 (6H, t, J =7.4 Hz).

ES/MS: 366.3 (M+NH4), 347.2 (m-1).

D. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methylsulfonyloxy-phenyl]pentane.



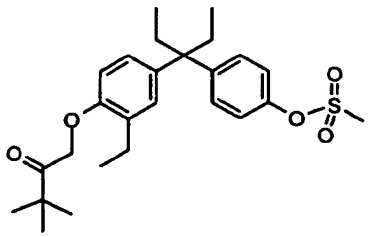
Using a procedure analogous to Example 36D, 3'-(4-hydroxy-3-methylphenyl)-3'-(4-methylsulfonyloxy-phenyl)pentane (0.17g, 0.5 mmol) gives the title compound (0.14 g, 63%).

H-NMR (300 mHz, DMSO-d6): δ 7.25 (4H, s), 6.92 (1H, s), 6.88 (1H, d, J = 8.2 Hz), 6.61 (1H, d, J = 8.2 Hz), 5.06 (2H, s), 3.35 (3H, s), 2.14 (3H, s), 2.04 (4H, q, J = 8.2 Hz), 1.16 (9H, s), 0.54 (6H, t, J = 8.2 Hz).

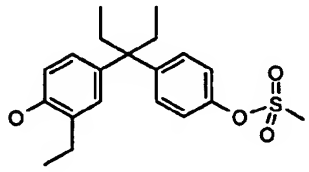
FAB/MS: 446.2 (M+).

Example 39

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-[4-methylsulfonyloxy-phenyl]pentane.



A. 3'-(4-Hydroxy-3-ethylphenyl)-3'-(4-methylsulfonyloxy-phenyl)pentane.

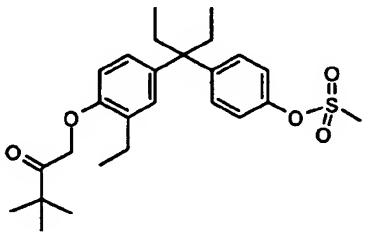


Using a procedure analogous to Example 36A, z/e-3'-(4-methylsulfonyloxyphenyl)-3'-pentene (0.2 g, 0.8 mmol) gives the title compound (0.135 g, 45%).

H-NMR (400 mHz, CDCl3): 7.20 (2H, d, J = 8.8 Hz), 7.14 (2H, d, J = 8.8 Hz), 6.88 (1H, s), 6.80 (1H, d, J = 8.4 Hz), 6.64 (1H, d, J = 8.4 Hz), 4.60 (1H, m), 3.11 (3H, s), 2.56 (2H, q, J = 7.2 Hz), 2.03 (4H, m), 1.16 (3H, t, J = 7.2 Hz), 0.60 (6H, t, J = 7.4 Hz).

ES/MS: 380.2 (M+NH4), 361.1 (m-1).

B. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-[4-methylsulfonyloxy-phenyl]pentane.

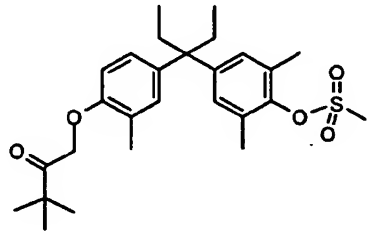


Using a procedure analogous to Example 36D, 3'-(4-hydroxy-3-ethylphenyl)-3'-(4-methylsulfonyloxy-phenyl)pentane (0.14g, 0.4 mmol) gives the title compound (70 mg, 40 %).

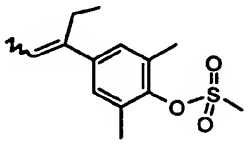
H-NMR (300 mHz, DMSO-d6): δ 7.25 (4H, s), 6.92 (1H, s), 6.88 (1H, d, J = 8.2 Hz), 6.62 (1H, d, J = 8.2 Hz), 5.06 (2H, s), 3.35 (3H, s), 2.55 (2H, q, J = 6.8 Hz), 2.04 (4H, q, J = 6.8 Hz), 1.16 (9H, s), 1.07 (3H, t, J = 6.8 Hz), 0.54 (6H, t, J = 6.8 Hz).

Example 40

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[3,5-dimethyl-4-methylsulfonyloxy-phenyl]pentane.



A. z/e-3'-(3,5-Dimethyl-4-methylsulfonyloxyphenyl)-3'-pentene.

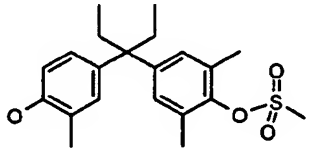


Using a procedure analogous to Example 36C, 3'-(3,5-dimethyl-4-methoxyphenyl)-3'-pentanol (2.2 g, 10 mmol) is reacted for 3 h to give crude z/e-3'-(3,5-dimethyl-4-hydroxyphenyl)-3'-pentene [ES/MS: 191.1 (M+1) 189.1 (M-1)]. Using a procedure analogous to Example 36B, crude z/e-3'-(3,5-dimethyl-4-hydroxyphenyl)-3'-pentene gives the title compound (2.12 g, 79% crude).

H-NMR (400 mHz, CDCl3): 5.68 (0.7 H, q, J = 6.6 Hz), 5.48 (0.3 H, q, J = 6.6 Hz).

ES/MS: 269.1 (M+1)

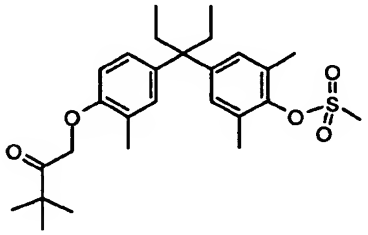
B. 3'-(4-Hydroxy-3-methylphenyl)-3'-(3,5-dimethyl-4-methylsulfonyloxy-phenyl)pentane.



Using a procedure analogous to Example 36A, z/e-3'-(3,5-dimethyl-4-methylsulfonyloxyphenyl)-3'-pentene (0.27 g, 1 mmol) gives the title compound (0.29 g, 76 %).

H-NMR (400 mHz, CDCl3): 6.8-6.9 (4H, m), 6.64 (2H, d, J = 8.4 Hz), 4.60 (1H, m), 3.25 (3H, s), 2.30 (6H, s), 2.19 (3H, s), 1.99 (4H, q, J = 7.2 Hz), 0.58 (6H, t, J = 7.2 Hz).
ES/MS: 394.3 (M+NH4), 375.1 (m-1).

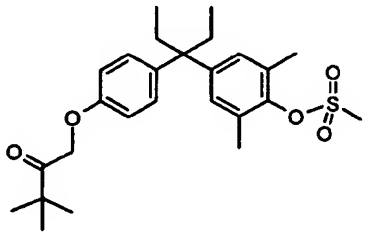
C. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[3,5-dimethyl-4-methylsulfonyloxy-phenyl]pentane.



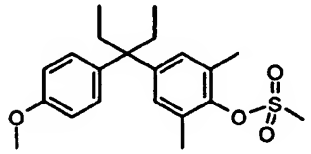
Using a procedure analogous to Example 36D, 3'-(4-hydroxy-3-methylphenyl)-3'-(3,5-dimethyl-4-methylsulfonyloxy-phenyl)pentane (0.29 g, 0.76 mmol) gives the title compound (176 mg, 49 %).
H-NMR (300 mHz, DMSO-d6): δ 6.83-6.95 (4H, m), 6.61 (1H, d, J = 7.5 Hz), 5.05 (2H, s), 3.26 (3H, s), 2.30 (6H, s), 2.24 (3H, s), 2.00 (4H, q, J = 6.8 Hz), 1.15 (9H, s), 1.07 (3H, t, J = 6.8 Hz), 0.51 (6H, t, J = 6.8 Hz).
FAB/MS: 474.1 (M+).

Example 41

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-phenyl]-3'-[3,5-dimethyl-4-methylsulfonyloxy-phenyl]pentane.



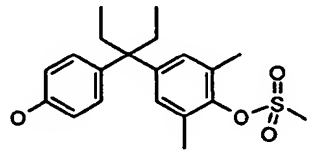
A. 3'-(4-Methoxyphenyl)-3'-(3,5-dimethyl-4-methylsulfonyloxy-phenyl)pentane.



Using a procedure analogous to Example 36A, z/e-3'-(3,5-dimethyl-4-methylsulfonyloxyphenyl)-3'-pentene (0.27 g, 1 mmol) and anisole (0.54 g, 5 mmol) are reacted for 64 h to give the title compound (0.22 g, 58%).

H-NMR (400 mHz, CDCl3): 7.04 (2H, d, J = 8.8 Hz), 6.84 (2H, s), 6.78 (2H, d, J = 8.8 Hz), 3.78 (3H, s), 3.26 (3H, s), 2.30 (6H, s), 2.01 (4H, q, J = 7.2 Hz), 0.59 (6H, t, J = 7.2 Hz).

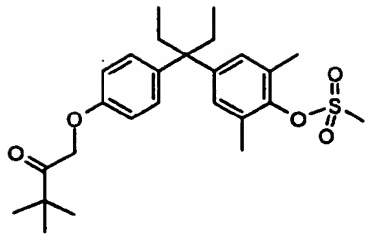
B. 3'-(4-Hydroxyphenyl)-3'-(3,5-dimethyl-4-methylsulfonyloxy-phenyl)pentane.



Using a procedure analogous to Example 36C, 3'-(4-methoxyphenyl)-3'-(3,5-dimethyl-4-methylsulfonyloxy-phenyl)pentane (0.22 g, 0.6 mmol) is reacted for 8 h to give the title compound (0.2 g, 95%).

H-NMR (400 mHz, CDCl3): 7.00 (2H, d, J = 8.8 Hz), 6.84 (2H, s), 6.71 (2H, d, J = 8.8 Hz), 4.60 (1H, s), 3.26 (3H, s), 2.30 (6H, s), 2.00 (4H, q, J = 7.6 Hz), 0.58 (6H, t, J = 7.6 Hz).

C. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-phenyl]-3'-[3,5-dimethyl-4-methylsulfonyloxy-phenyl]pentane.



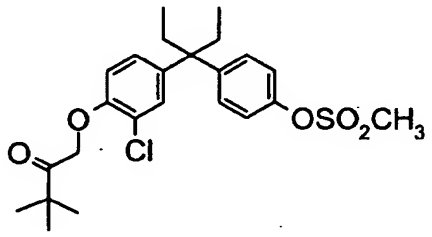
Using a procedure analogous to Example 36D, 3'-(4-hydroxyphenyl)-3'-(3,5-dimethyl-4-methylsulfonyloxy-phenyl)pentane (0.19 g, 0.54 mmol) gives the title compound (173 mg, 70 %).

H-NMR (300 mHz, DMSO-d6): δ 7.04 (2H, d, J = 8.2 Hz), 6.90 (2H, s), 6.75 (2H, d, J = 8.2 Hz), 5.04 (2H, s), 3.26 (3H, s), 2.24 (6H, s), 2.02 (4H, q, J = 7.0 Hz), 1.15 (9H, s), 0.53 (6H, t, J = 7.0 Hz).

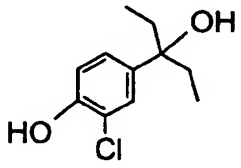
ES/MS: 478.3 (M+NH4).

Example 42

Preparation of 3'-[3-chloro-4-(2-oxo-3,3-dimethylbutoxy)phenyl]-3'-[4-(methylsulfonyloxy)phenyl]pentane.



A. 3-(3-Chloro-4-hydroxyphenyl)-3-pentanol.



To a solution of methyl 3-chloro-4-hydroxybenzoate (25.0 g, 133 mmol) in THF (250 mL) is added dropwise 1.0 M ethylmagnesium bromide/THF (442 mL, 442 mmol) at

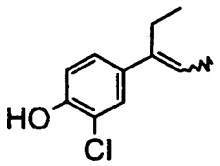
a rate maintaining the temperature below 27 °C. The brownish grey reaction is stirred for 72 h. The reaction mixture is cooled in an ice bath and quenched with satd ammonium chloride (1 ml portions) until evolution of ethane subsides. Additional satd NH_4Cl solution is added (total of 50mL) and the mixture is concentrated to remove most of the THF. The residue is added to water and ether, filtered through diatomaceous earth, and partitioned. The organic layer is washed with brine (3 X), $MgSO_4$ dried, and concentrated to give the title compound (28.6 g, 99%).

H-NMR (300 mHz, CDCl3): δ 7.38 (1H, d, J = 1.6 Hz), 7.07 (1H, dd, J = 8.4 Hz, J = 1.6 Hz), 6.95 (1H, d, J = 8.4 Hz), 5.53 (1H, br s), 1.80 (4H, m), 0.76 (6H, t, J = 7.6 Hz).

IR (CHCl3): 3600 cm^{-1}, 3540 cm^{-1}1

TOF MS EI+ 214.076; Calc. m/z. 214.0761

B. [E, Z]-3-(3-Chloro-4-hydroxyphenyl)-3-pentene

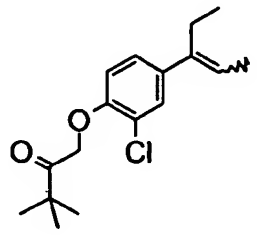


A mixture of 3-(3-chloro-4-hydroxyphenyl)-3-pentanol (10.0 g, 46.5 mmol), pTSA monohydrate (20 mg, catalytic amount), and toluene (300 mL) is heated on a steam bath for 3 h. The toluene solution is cooled to RT, washed with satd sodium carbonate solution (25 mL), $MgSO_4$ dried, and concentrated to give the title compounds as a [E:Z] isomeric mixture of [85:15] (9.2 g, quant).

TLC (CHCl3): Rf ~0.7

H-NMR (300 mHz, DMSO-d6): δ 6.85-7.30 (3H, m), 5.65 (0.85H, q, J = 6.8 Hz), 5.43 (0.15H, q, J = 6.8 Hz), 2.43((1.7H, q, J = 7.6 Hz), 2.28 (0.3H, q, J = 7.6 Hz), 1.72 (2.55H, d, J = 7.6 Hz), 1.52 (0.45H, d, J = 7.6 Hz), 0.90 (2.55H, t, J = 7.6 Hz)), 0.85 (0.45H, t, J = 7.6 Hz)..

C. [E,Z]-3-[3-Chloro-4-(2-oxo-3,3-dimethylbutoxy)phenyl]-3-pentene

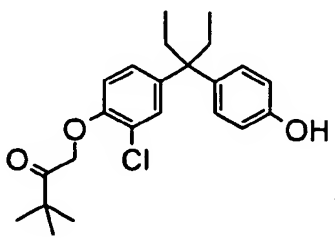


A mixture of [E,Z]-3-(3-Chloro-4-hydroxyphenyl)-3-pentene (4.00 g, 20.3 mmol) and 1-chloropinacolone (2.73 g, 20.3 mmol), anhydrous KI (0.17 g, 1.0 mmol), K_2CO_3 (14.0 g, 102 mmol) and acetonitrile (80 mL) is refluxed for 3 h. The reaction is cooled to RT and concentrated. The residue is partitioned between methylene chloride (50 mL) and ice water (50 mL). The organic layer is $MgSO_4$ dried, concentrated, and chromatogrpahed (40% to 70% chloroform in hexane) to give the title compounds as an 85 : 15 [E. Z] mixture (5.07 g, 85%).

H-NMR (300 mHz, DMSO-d6): δ 7.37 (0.85H, d, J = 2.1 Hz), 7.22 (0.85H, dd, J=2.1, J = 8.6 Hz), 7.18 (0.15H, d, J = 2.1 Hz), 7.03 (0.15H, dd, J = 2.0 Hz, J = 8.4 Hz), 6.88 (0.15H, d, J = 8.4 Hz), 6.85 (0.85H, d, J = 8.6 Hz), 5.71 (0.85H, m), 5.52 (0.15H, m), 5.25 (2H, s), 2.45 (1.70H, q, J = 7.6 Hz), 2.30 (0.30H, q, J = 7.6 Hz), 1.75 (2.55H, d, J = 7.6 Hz), 1.53 (0.45H, d, J = 7.6 Hz), 1.17 (9H, s), 0.91 (2.55H, t, J = 7.6 Hz), 0.88 (0.45H, t, J = 7.6 Hz).

TOF MS EI+ : 294.139; Calc. m/z 294.1387.

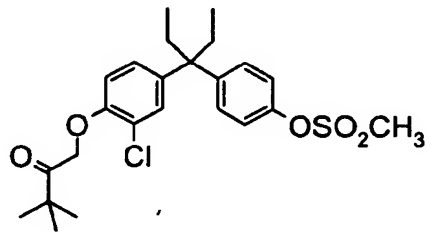
D. 3'-[3-Chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-hydroxyphenyl)pentane.



A -20 °C solution of [E,Z]-3-[3-chloro-4-(2-oxo-3,3-dimethylbutoxy)phenyl]-3-pentene (4.5 g, 15.2 mmol), phenol (17.2 g, 183 mmol) and methylene chloride (30 mL) is treated with BF3-etherate (0.863 g, 6.1 mmol) and stirred for 30 m while maintaining the temperature near –20 °C. The resulting light reddish brown solution is allowed to warm to 0 °C and kept at that temperature for 16 h. The reaction is distilled at 45 °C/0.04 mm to remove most of the excess phenol. The residue is treated with powderized $NaHCO_3$ (600 mg), ethylene glycol (15 ml), and distilled to remove the last of the phenol and almost all of the glycol. The resulting viscous tan oily residue is cooled to RT and distributed between sat $NaHCO_3$ (25 mL) and ethyl acetate (200 mL). The organic layer is separated, washed with water (5 x 50 mL), Na_2SO_4 dried, and concentrated to give the title compound as an oil (5.8 g, 98%).

H-NMR (300 mHz, CDCl3): 7.21 (1H, d, J = 2.3 Hz), 6.99 (2H, d, J = 8.7 Hz), 6.95 (1H, dd, J = 2.3 Hz, J = 8.6 Hz), 6.75 (2H, d, J = 8.7 Hz), 6.62 (1H, d, J = 8.6 Hz), 4.91 (2H, s), 4.86 (1H, s), 2.02 (4H, q, J = 7.3 Hz), 1.28 (9H, s), 0.62 (6H, t, J = 7.3 Hz).
ES(+) MS m/z: 389.3 (M+H); calc. m/z 389.1883 (M+H).

E. 3'-[3-Chloro-4-(2-Oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-methylsulfonyloxyphenyl)pentane.



Using a procedure analogous to Example 17 with brine and satd $NaHCO_3$ washes, 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-hydroxyphenyl)pentane gives the title compound as a colorless oil (1.16 g., 97 %).

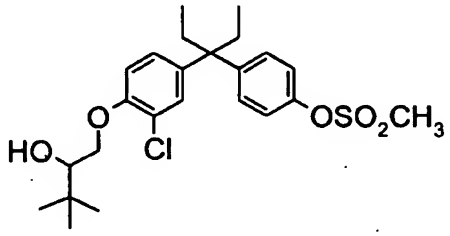
H-NMR (300 mHz, CDCl3): δ 7.15-7.20 (1H, m), 6.91 (2H, dd, J = 2.3 Hz, J = 8.7 Hz), 6.61 (1H, d, J = 8.7 Hz), 4.91 (2H, s), 3.14 (3H, s), 2.04 (4H, q, J = 7.4 Hz), 1.26 (9H, s), 0.62 (6H, t, J = 7.4 Hz).

IR (CHCl3) 1727.91 cm-1.

ES(+) MS m/z: 489.2 (M+Na); Calc. m/z 489.1478 (M+Na).

Example 43

Preparation of racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(4-methylsulfonyloxyphenyl)pentane.



Using a procedure analogous to Example 1C with acetone quench, 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-methylsulfony-oxyphenyl)pentane gives the title compound as an oil (646 mg, 99%).

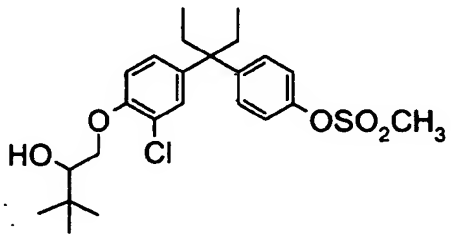
H-NMR (300 mHz, DMSO-D6): δ 7.0-7.3 (7H, m), 4.74 (1H, d), 4.11 (1H, dd), 3.86 (1H, dd), 4.97 (1H, m), 3.36 (3H, s), 3.32 (1H, s), 2.06 (4H, q, J = 7.3 Hz), 0.93 (9H, s), 0.57 (6H, t, J = 7.3 Hz).

IR (CHCl3): 3587.94 cm-1.

ES(+) MS m/z: 486.3 (M+NH4), 491.2 (M+Na); Calc. 486,2081 (M+NH4), 491.1713 (M+Na).

Example 44 and Example 45

Preparation of enantiomers of 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(4-methylsulfonyloxyphenyl)pentane.



A racemic mixture 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(4-methylsulfonyloxyphenyl)pentane (558 mg) is chromatographed with a Chiralcel AD column to give enantiomer 1, Example 44 (199 mg, 36%) and enantiomer 2, Example 45 (193 mg, 35%).

Enantiomer 1, Example 44

HPLC: Chiralpak AD (4.6 X 150 mm); 100% 3A Alcohol; 0.6 mL/m (flow rate); rt = 6.1 m; 240 nm; ee 100% by HPLC.

H-NMR (300 mHz, CDCl3): δ 7.1-7.3 (5H, m), 6.95 (1H, dd, J = 2.1, J= 8.6), 6.83 (1H, d, J = 8.6), 4.17 (1H, dd), 3.88 (1H, t), 3.72 (1H, m), 3.17 (3H, s), 2.58 (1H, d), 2.05 (4H, q, J = 7.3 Hz), 1.03 (9H, s), 0.62 (6H, t, J = 7.3 Hz).

FAB(+) MS m/z [M]: 468.2; calc. m/z 468.1737.

Enantiomer 2, Example 45

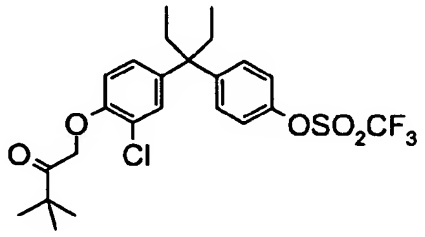
HPLC: Chiralpak AD (4.6 X 150 mm); 100% 3A Alcohol; 0.6 mL/m (flow rate); rt = 8.6 m; 240 nm; ee 98.4% by HPLC.

H-NMR (300 mHz, CDCl3): δ 7.1-7.3 (5H, m), 6.95 (1H, dd, J = 2.1, J= 8.6), 6.83 (1H, d, J = 8.6), 4.17 (1H, dd), 3.88 (1H, t), 3.72 (1H, m), 3.17 (3H, s), 2.58 (1H, d), 2.05 (4H, q, J = 7.3 Hz), 1.03 (9H, s), 0.62 (6H, t, J = 7.3 Hz).

FAB(+) MS m/z [M]: 468.3; calc. m/z 468.1737.

Example 46

Preparation of 3'-[3-chloro-4-(2-Oxo-3.3-dimethylbutoxy)]-3'-(4-trifluoromethylsulfonyloxyphenyl)pentane.



Using a procedure analogous to Example 17 at RT with potassium phosphate monobasic/sodium hydroxide buffer quench, 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-hydroxyphenyl)pentane and triflic anhydride give the title compound as a colorless oil (3.7g, 69%).

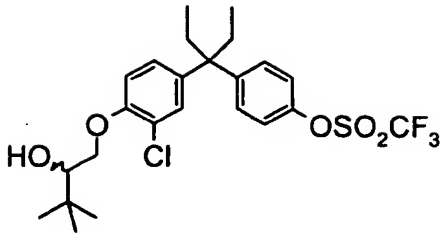
H-NMR (300 mHz, DMSO-D6): δ 7.40 (2H, d, J = 8.7 Hz), 7.33 (2H, d, J = 8.7 Hz), 7.15 (1H, d, J = 2.1 Hz), 6.68 (1H, dd, J = 2.1 Hz, J = 8.6 Hz), 6.78 (2H, d, J = 8.6 Hz), 5.22 (2H, s), 2.07 (4H, q, J = 7.3 Hz), 1.17 (9H, s), 0.62 (6H, t, J = 7.3 Hz).

FAB+ MS: 521.0 (M+H); calc. 521.1376 (M+H).

ES MS: 521.3 (M+1), 538.3 (M+NH4), 543.2 (M+Na)

Example 47

Preparation of 3'-[3-chloro-4-(2-hydroxy-3.3-dimethylbutoxy)phenyl]-3'-(4-trifluoromethylsulfonyloxyphenyl)pentane.



Using a procedure analogous to Example 1C, 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-trifluoromethylsulfonyloxyphenyl)pentane gives the title compound as a colorless oil (495 mg, 99%).

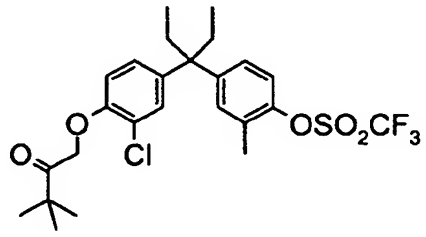
H-NMR (300 mHz, CDCl3): δ 7.21 (2H, d, J = 8.8 Hz), 7.16 (2H, d, J = 8.8 Hz), 6.97 (1H, dd, J = 2.3 Hz, J = 8.6 Hz), 6.84 (1H, d, J = 8.6 Hz), 4.18 (1H, dd, J = 2.6 Hz, J = 9.0 Hz), 3.89 (t, J = 8.9 Hz,), 3.73 (1H, dt, J = 2.6, J = 8.9, J = 3.0), 2.57, (1H, d, J = 3.0 Hz), 2.06 (4H, q, J = 7.3 Hz), 1.04 (9H, s), 0.62 (6H, t, J = 7.3 Hz).

FAB(+) MS m/z [M]: 522.1; calc. 522.1455.

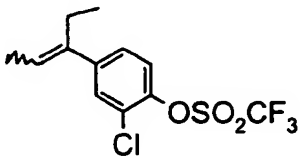
ES (+) MS m/z: 540.3 (M+NH4); calc 540.1798.

Example 48

Preparation of 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(trifluoromethylsulfonyloxy)phenyl]pentane.



A. [E,Z]-3-[3-Chloro-4-(trifluoromethylsulfonyloxy)phenyl)-3-pentene.

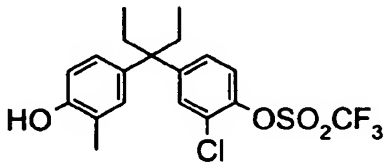


Using a procedure analogous to Example 17, [E,Z]-3-(3-chloro-4-hydroxyphenyl)-3-pentene, triflic anhydride, and diisopropylethylamine give the title compound as a brown oil in a [E:Z] ratio of 3:1 (8.7 g, quant).

H-NMR (300 mHz, CDCl3): δ 7.01-7.40 (3H, m), 5.67 (0.75H, q, J = 6.9 Hz), 5.53 (0.25H, q, J = 6.9 Hz), 2.41((1.5H, q, J = 7.6 Hz), 2.24 (0.5H, q, J = 7.6 Hz), 1.84 (2.25H, d, J = 7.6 Hz), 1.48 (0.75H, d, J = 7.6 Hz), 0.91 (2.25H, t, J = 7.6 Hz)), 0.86 (0.75H, t, J = 7.6 Hz).

TOF MS EI+ :328.015; calc. 328.0226.

B. 3'-(4-hydroxy-3-methylphenyl)-3'-[3-chloro-4-(methylsulfonyloxy)-phenyl]pentane.



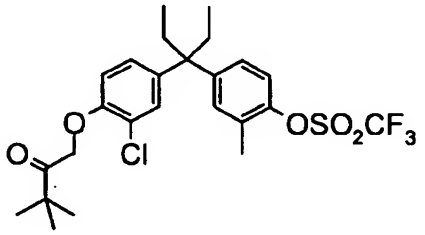
Using a procedure analogous to Example 42D, [E,Z]-3-[3-chloro-4-(trifluoromethylsulfonyloxy)phenyl]-3-pentene and o-cresol give the title compound as a pale tan oil (4.29g, 38%).

H-NMR (300 mHz, CDCl3): 6.5 to 7.3 (6H, m) 4.57 (1H,s), 2.21 (3H, s), 2.05 (4H, q, J = 7.3 Hz), 0.62 (6H, t, J =7.3 Hz).

ES(-) MS m/z: 435.1 (M-H); calc. 435.0645.

C. Preparation of 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)-phenyl]-3'-[3-methyl-4-(trifluoromethylsulfonyloxy)phenyl]pentane.

NOTE: Triflate Rearrangement Procedure



Using a procedure analogous to Example 42C, 3'-(3-chloro-4-hydroxyphenyl)-3'-[3-methyl-4-(methylsulfonyloxy)phenyl]pentane and chromatographies (30% to 50% chloroform/Hex; Hex to 10% EtOAc/Hex) to give the title compound (2.61 g, 53%).

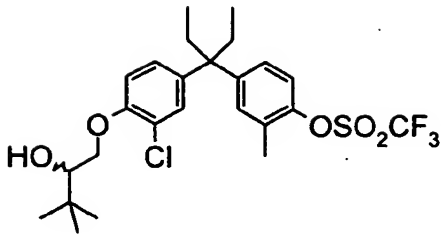
H-NMR (300 mHz, CDCl3): δ 7.15 (1H, d, J = 2.3 Hz), 7.11 (1H, d, J= 8.4 Hz), 7.04 (1H, d, J = 2.3 Hz), 7.02 (1H, dd, J = 2.3 Hz, J = 8.4 Hz), 6.89 (1H, dd, J = 8.6 Hz, J = 2.3 Hz), 6.62 (1H, d, J = 8.6 Hz), 4.91 (2H, s), 2.32 (3H, s), 2.03 (4H, q, J = 7.2 Hz), 1.26 (9H, s), 0.60 (6H, t, J = 7.2 Hz).

ES(+) MS m/z: 552.2 (M+NH4); calc. 552.1798

FAB(+) MS m/z [M]: 534.9; calc. 534.

Example 49

Preparation of 3'-[3-chloro-4-(2-hydroxy-3.3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(trifluoromethylsulfonyloxy)phenyl]pentane.



Using a procedure analogous to Example 1C, 3'-[3-chloro-4-(2-oxo-3,3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(methylsulfonyloxy)phenyl]pentane gives the title compound (719 mg, 98%).

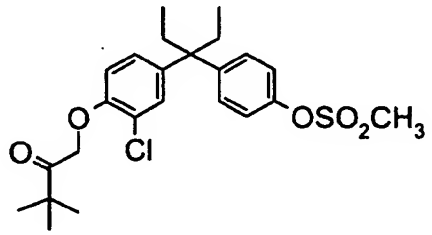
H-NMR (300 mHz, CDCl3): δ 7.15 (1H, d, J = 2.3 Hz), 7.13 (1H, d, J= 8.4 Hz), 7.05 (1H, d, J = 2.0 Hz), 7.03 (1H, dd, J = 2.3 Hz, J = 8.4 Hz), 6.96 (1H, dd, J = 8.6 Hz, J = 2.3 Hz), 6.86 (1H, d, J = 8.6 Hz), 4.20 (1H, dd, J = 8.9, 2.5 Hz), 3.906 (1H, t, J = 8.9 Hz), 3.75 (1H, dd, J = 8.9, 2.5 Hz), 2.59 (1H, br s), 2.34 (3H, s), 2.06 (4H, q, J = 7.3 Hz), 1.03 (9H, s), 0.63 (6H, t, J = 7.3 Hz).

ES(+) MS m/z: 554.2 (M+NH4); calc. 554.1954.

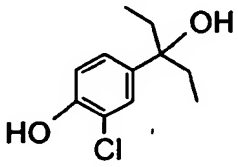
FAB(+) MS m/z [M]: 536.1; calc. 536.1661

Example 50

Preparation of 3'-[3-chloro-4-(2-oxo-3,3-dimethylbutoxy)phenyl]-3'-[4-(methylsulfonyloxy)phenyl]pentane.



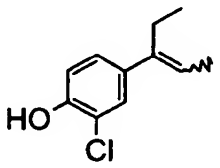
A. 3-(3-Chloro-4-hydroxyphenyl)-3-pentanol.



To a solution of methyl 3-chloro-4-hydroxybenzoate (25.0 g, 133 mmol) in THF (250 mL) is added dropwise 1.0 M ethylmagnesium bromide in THF (442 mL, 442 mmol) so as to maintain the temperature below 27 °C. The resulting brownish grey solution is allowed to stir for 72 h during which time a cream-colored gelatinous precipitate is formed. The reaction mixture is cooled in an ice bath and quenched with 1 mL portions of sat. ammonium chloride solution until evolution of ethane subsides. Additional NH_4Cl solution is added (to a total of 50mL) and the resulting mixture is concentrated to remove most of the THF. The resulting residue is distributed into water and ether and filtered through diatomaceous earth to break the partial emulsion that forms. The organic layer is washed 3 times with sat. NaCl, dried over anhydrous magnesium sulfate and concentrated under vacuum to give the title compound (28.6 g, 99%).

H-NMR (300 mHz, CDCl3): δ 7.38 (1H, d, J = 1.6 Hz), 7.07 (1H, dd, J = 8.4 Hz, J = 1.6 Hz), 6.95 (1H, d, J = 8.4 Hz), 5.53 (1H, br s), 1.80 (4H, m), 0.76 (6H, t, J = 7.6 Hz).
IR (CHCl3): 3600 cm^{-1}, 3540 cm^{-1}1
TOF MS EI+ 214.076; Calc. m/z. 214.0761

B. [E, Z]-3-(3-Chloro-4-hydroxyphenyl)-3-pentene

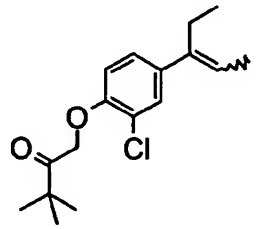


A mixture of 3-(3-chloro-4-hydroxyphenyl)-3-pentanol (10.0 g, 46.5 mmol), p-toluene sulfonic acid monohydrate (20 mg, catalytic amount), and toluene (300 mL) are heated on a steam bath for 3 h. Analysis by TLC (silica gel, $CHCL_3$) shows loss of the starting material and formation of a more mobile spot at Rf ~0.7. The toluene solution is allowed to cool to RT and is washed with sat. sodium carbonate solution (25 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gives the title mixture of [E, Z]-isomeric compounds in a ratio of

approximately 85 : 15, respectively (9.2 g, 100%). The product can be used without further purification.

H-NMR (300 mHz, DMSO-d6): δ 6.85-7.30 (3H, m), 5.65 (0.85H, q, J = 6.8 Hz), 5.43 (0.15H, q, J = 6.8 Hz), 2.43((1.7H, q, J = 7.6 Hz), 2.28 (0.3H, q, J = 7.6 Hz), 1.72 (2.55H, d, J = 7.6 Hz), 1.52 (0.45H, d, J = 7.6 Hz), 0.90 (2.55H, t, J = 7.6 Hz)), 0.85 (0.45H, t, J = 7.6 Hz)..

C. [E,Z]-3-[3-Chloro-4-(2-oxo-3,3-dimethylbutoxy)phenyl]-3-pentene



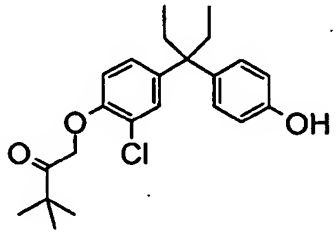
[E,Z]-3-(3-Chloro-4-hydroxyphenyl)-3-pentene (4.00 g, 20.3 mmol) and 1-chloropinacolone (2.73 g, 20.3 mmol), anhydrous KI (0.17 g, 1.0 mmol), K2CO3 (14.0 g, 102 mmol) and acetonitrile (80 mL) are combined and heated at reflux for 3 h. The reaction mixture is allowed to cool to RT and most of the solvent is removed by concentration under reduced pressure. The resulting solid residue is distributed between methylene chloride (50 mL) and ice water (50 mL) and the layers are separated. The organic layer is dried over anhydrous magnesium sulfate and concentrated to provide an oil, ~ 6.0 g. The crude product is purified by silica gel chromatography using a gradient of 40% to 70% chloroform in hexane. Concentration of fractions containing either or both of the desired isomers provides the title compounds as an 85 : 15 [E. Z] mixture, respectively (5.07 g, 85%).

H-NMR (300 mHz, DMSO-d6): δ 7.37 (0.85H, d, J = 2.1 Hz), 7.22 (0.85H, dd, J=2.1, J = 8.6 Hz), 7.18 (0.15H, d, J = 2.1 Hz), 7.03 (0.15H, dd, J = 2.0 Hz, J = 8.4 Hz), 6.88 (0.15H, d, J = 8.4 Hz), 6.85 (0.85H, d, J = 8.6 Hz), 5.71 (0.85H, m), 5.52 (0.15H, m), 5.25

(2H, s), 2.45 (1.70H, q, J = 7.6 Hz), 2.30 (0.30H, q, J = 7.6 Hz), 1.75 (2.55H, d, J = 7.6 Hz), 1.53 (0.45H, d, J = 7.6 Hz), 1.17 (9H, s), 0.91 (2.55H, t, J = 7.6 Hz), 0.88 (0.45H, t, J = 7.6 Hz).

TOF MS EI+ : 294.139; Calc. m/z 294.1387.

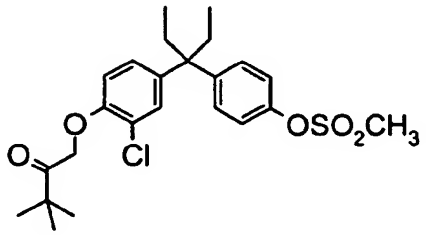
D. 3'-[3-Chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-hydroxyphenyl)pentane.



A solution of [E,Z]-3-[3-chloro-4-(2-oxo-3,3-dimethylbutoxy)phenyl]-3-pentene (4.5 g, 15.2 mmol) and phenol (17.2 g, 183 mmol) in methylene chloride (30 mL) is carefully cooled to -20 °C so as not to cause crystallization of the phenol. The cold solution is treated with BF_3-etherate (0.863 g, 6.1 mmol) and the resulting mixture is stirred for 30 m while the temperature is maintained near –20 °C. The resulting light reddish brown solution is then allowed to warm to 0 °C and kept at that temperature for 16 h. The reaction mixture is placed under vacuum (0.04 mm, 45 °C oil bath) and distilled to remove most of the excess phenol. When the distillation slows, the residue is treated with powdered $NaHCO_3$ (600 mg) and ethylene glycol (15 ml) and the distillation is resumed to remove the last of the phenol and almost all of the glycol. The resulting viscous tan oily residue is cooled to RT and distributed between sat $NaHCO_3$ (25 mL) and ethyl acetate (200 mL). The organic layer is separated and washed with water (5 x 50 mL), dried over anhydrous sodium sulfate and concentrated to give the title product as a nearly colorless oil (5.8 g, 98%) which requires no further purification.

H-NMR (300 mHz, CDCl3): 7.21 (1H, d, J = 2.3 Hz), 6.99 (2H, d, J = 8.7 Hz), 6.95 (1H, dd, J = 2.3 Hz, J = 8.6 Hz), 6.75 (2H, d, J = 8.7 Hz), 6.62 (1H, d, J = 8.6 Hz), 4.91 (2H, s), 4.86 (1H, s), 2.02 (4H, q, J = 7.3 Hz), 1.28 (9H, s), 0.62 (6H, t, J = 7.3 Hz).
ES(+) MS m/z: 389.3 (M+H); calc. m/z 389.1883 (M+H).

E. 3'-[3-Chloro-4-(2-Oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-methylsulfonyloxyphenyl)pentane.

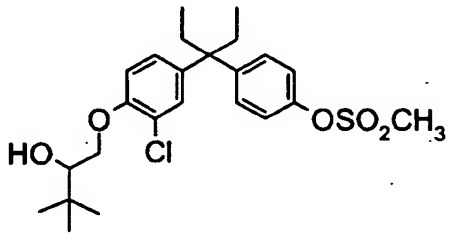


To 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-hydroxyphenyl)pentane (1.00 g, 2.57 mmol) in methylene chloride (100mL) is added successively by syringe triethyl amine (0.390 g, 3.85 mmol) and methanesulfonyl chloride (0.368, 0.25 mL, 3.21 mmol). After stirring the reaction mixture for 2 h, it is concentrated to near dryness and the residue is distributed between EtOAc (125 mL) and 0.1 N HCl (50 mL). The organic layer is separated and washed with sat. NaCl and with sat. $NaHCO_3$, dried over anhydrous magnesium sulfate and, concentrated. Drying of the residue under high vacuum provides the title compound as a colorless oil (1.16 g., 97 %).
H-NMR (300 mHz, CDCl3): δ 7.15-7.20 (1H, m), 6.91 (2H, dd, J = 2.3 Hz, J = 8.7 Hz), 6.61 (1H, d, J = 8.7 Hz), 4.91 (2H, s), 3.14 (3H, s), 2.04 (4H, q, J = 7.4 Hz), 1.26 (9H, s), 0.62 (6H, t, J = 7.4 Hz).
IR (CHCl3) 1727.91 cm-1.

ES(+) MS m/z: 489.2 (M+Na); Calc. m/z 489.1478 (M+Na).

Example 51

Preparation of racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(4-methylsulfonyloxyphenyl)pentane.



To 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-methylsulfonyoxyphenyl)pentane (650 mg, 1.39 mmol) in 45 mL of MeOH at 0 °C. is added sodium borohydride (55.4 mg, 1.46 mmol). The reaction mixture is allowed to warm to RT and after 16h the excess reagent is destroyed by the addition of acetone (1 ml.). The resulting solution is concentrated to near dryness under reduced pressure and the residue is distributed between methylene chloride (20 mL) and water (20 mL). The organic layer is separated and the aqueous layer is extracted with additional methylene chloride (10 mL). The combined organic extracts are dried over anhydrous sodium sulfate and concentrated to an oil which is the title compound (646 mg, 99%).

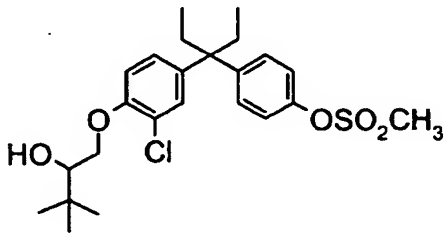
H-NMR (300 mHz, DMSO-D6): δ 7.0-7.3 (7H, m), 4.74 (1H, d), 4.11 (1H, dd), 3.86 (1H, dd), 4.97 (1H, m), 3.36 (3H, s), 3.32 (1H, s), 2.06 (4H, q, J = 7.3 Hz), 0.93 (9H, s), 0.57 (6H, t, J = 7.3 Hz).

IR (CHCl3): 3587.94 cm-1.

ES(+) MS m/z: 486.3 (M+NH4), 491.2 (M+Na); Calc. 486,2081 (M+NH4), 491.1713 (M+Na).

for Example 51A and Example 51B

Preparation of enantiomers of 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(4-methylsulfonyloxyphenyl)pentane.



A racemic mixture 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(4-methylsulfonyloxyphenyl)pentane (558 mg) is chromatographed with a Chiralcel AD column to give enantiomer 1, Example 2A (199 mg, 36%) and enantiomer 2, Example 2B (193 mg, 35%).

for Enantiomer 1, Example 51A

HPLC: Chiralpak AD (4.6 X 150 mm); 100% 3A Alcohol; 0.6 mL/m (flow rate); rt = 6.1 m; 240 nm; ee 100% by HPLC.

H-NMR (300 mHz, CDCl3): δ 7.1-7.3 (5H, m), 6.95 (1H, dd, J = 2.1, J= 8.6), 6.83 (1H, d, J = 8.6), 4.17 (1H, dd), 3.88 (1H, t), 3.72 (1H, m), 3.17 (3H, s), 2.58 (1H, d), 2.05 (4H, q, J = 7.3 Hz), 1.03 (9H, s), 0.62 (6H, t, J = 7.3 Hz).

FAB(+) MS m/z [M]: 468.2; calc. m/z 468.1737.

for Enantiomer 2, Example 51B

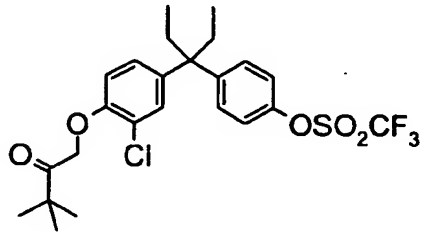
HPLC: Chiralpak AD (4.6 X 150 mm); 100% 3A Alcohol; 0.6 mL/m (flow rate); rt = 8.6 m; 240 nm; ee 98.4% by HPLC.

H-NMR (300 mHz, CDCl3): δ 7.1-7.3 (5H, m), 6.95 (1H, dd, J = 2.1, J= 8.6), 6.83 (1H, d, J = 8.6), 4.17 (1H, dd), 3.88 (1H, t), 3.72 (1H, m), 3.17 (3H, s), 2.58 (1H, d), 2.05 (4H, q, J = 7.3 Hz), 1.03 (9H, s), 0.62 (6H, t, J = 7.3 Hz).

FAB(+) MS m/z [M]: 468.3; calc. m/z 468.1737.

Example 52

Preparation of 3'-[3-chloro-4-(2-Oxo-3.3-dimethylbutoxy)]-3'-(4-trifluoromethylsulfonyloxyphenyl)pentane.



To 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-hydroxyphenyl)pentane. (4.00 g, 10.3 mmol) and diisopropylethylamine (1.40 g, 1.88 mL, 10.8 mmol) in 160 mL of methylene chloride is added by syringe trifluoromethanesulfonic anhydride (3.05 g, 1.82 mL,10.8 mmol) at RT. After stirring the mixture for 16 h, the resulting brown solution is poured over pH=7.00 potassium phosphate monobasic/sodium hydroxide buffer (150 mL) and ice (150 g). The organic layer is separated and washed with additional buffer (2 x 150 mL), dried over anhydrous magnesium sulfate, and concentrated to an almost colorless viscous oil (5.2 g). The oil was purified by chromatography over silica gel with a gradient of 25% to 75% of chloroform-hexane. Appropriate fractions are combined and concentrated to provide the title compound as a clear, colorless oil (3.7g, 69%).

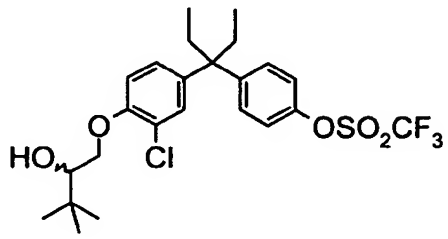
H-NMR (300 mHz, DMSO-D6): δ 7.40 (2H, d, J = 8.7 Hz), 7.33 (2H, d, J = 8.7 Hz), 7.15 (1H, d, J = 2.1 Hz), 6.68 (1H, dd, J = 2.1 Hz, J = 8.6 Hz), 6.78 (2H, d, J = 8.6 Hz), 5.22 (2H, s), 2.07 (4H, q, J = 7.3 Hz), 1.17 (9H, s), 0.62 (6H, t, J = 7.3 Hz).

FAB+ MS: 521.0 (M+H); calc. 521.1376 (M+H).

ES MS: 521.3 (M+1), 538.3 (M+NH4), 543.2 (M+Na)

Example 53

Preparation of racemic 3'-[3-chloro-4-(2-hydroxy-3.3-dimethylbutoxy)phenyl]-3'-(4-trifluoromethylsulfonyloxyphenyl)pentane.



To 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-trifluoromethylsulfonyloxyphenyl)pentane (500 mg, 0.96 mmol) in 40 mL of MeOH at 0 °C is added sodium borohydride (38 mg, 1.0 mmol). After 30 min at 0 °C. the excess reagent is destroyed by the addition of acetone (1 mL.) and pH=7.00 potassium phosphate monobasic/sodium hydroxide buffer (10 mL). The resulting mixture is concentrated to near dryness under reduced pressure and the residue is distributed between methylene chloride (20 mL) and water (20 mL). The organic layer is separated and the aqueous layer is extracted with additional methylene chloride (10 mL). The combined organic extracts are dried over anhydrous magnesium sulfate and concentrated to a colorless oil which is the title compound (495 mg, 99%).

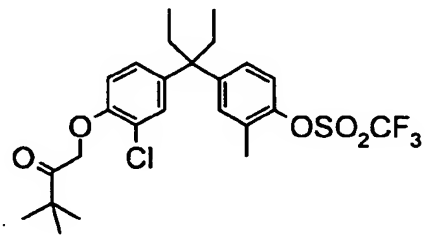
H-NMR (300 mHz, CDCl3): δ 7.21 (2H, d, J = 8.8 Hz), 7.16 (2H, d, J = 8.8 Hz), 6.97 (1H, dd, J = 2.3 Hz, J = 8.6 Hz), 6.84 (1H, d, J = 8.6 Hz), 4.18 (1H, dd, J = 2.6 Hz, J = 9.0 Hz), 3.89 (t, J = 8.9 Hz,), 3.73 (1H, dt, J = 2.6, J = 8.9, J = 3.0), 2.57, (1H, d, J = 3.0 Hz), 2.06 (4H, q, J = 7.3 Hz), 1.04 (9H, s), 0.62 (6H, t, J = 7.3 Hz).

FAB(+) MS m/z [M]: 522.1; calc. 522.1455.

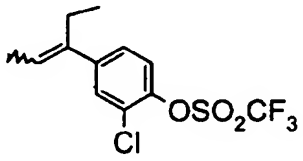
ES (+) MS m/z: 540.3 (M+NH4); calc 540.1798.

Example 54

Preparation of 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(trifluoromethylsulfonyloxy)phenyl]pentane.



A. [E,Z]-3-[3-Chloro-4-(trifluoromethylsulfonyloxy)phenyl)-3-pentene.



In a procedure analogous to Example 52, [E,Z]-3-(3-chloro-4-hydroxyphenyl)-3-pentene (5.15 g, 26 mmol), trifluoromethanesulfonic anhydride (8.13 g, 28 mmol), and diisopropylethylamine (3.7 g, 5.0 mL, 28 mmol) are reacted in 200 mL of methylene chloride to give the title compound as a brown oil (8.7 g, approx. 100%) which is used without further purification. The [E, Z} olefin isomers are present in a ratio of about 3 to 1, respectively.

H-NMR (300 mHz, CDCl3): δ 7.01-7.40 (3H, m), 5.67 (0.75H, q, J = 6.9 Hz), 5.53 (0.25H, q, J = 6.9 Hz), 2.41((1.5H, q, J = 7.6 Hz), 2.24 (0.5H, q, J = 7.6 Hz), 1.84 (2.25H, d, J = 7.6 Hz), 1.48 (0.75H, d, J = 7.6 Hz), 0.91 (2.25H, t, J = 7.6 Hz)), 0.86 (0.75H, t, J = 7.6 Hz).

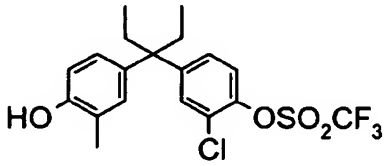
TOF MS EI+ :328.015; calc. 328.0226.

In an alternative preparation, a solution of [E,Z]-3-(3-chloro-4-hydroxyphenyl)-3-pentene (9.85 g, 50 mmol), and triethyl amine (5.32 g, 7.29 mL, 52 mmol) in 400 mL of methylene chloride at –35 deg C is treated slowly with trifluoromethanesulfonic anhydride (8.13 g, 28 mmol) added by syringe, so as to keep the temperature below minus 30 °C. The resulting pale yellow solution is stirred for 3 h while it is allowed to warm to RT. The reaction mixture is then poured over pH=7.00 potassium phosphate

monobasic/sodium hydroxide buffer (150 mL) and ice (150 g). The organic layer is separated and washed with additional buffer (4 x 150 mL), dried over anhydrous magnesium sulfate, and concentrated to a pale yellow oil (16.7 g, 98%). Final purification was accomplished by chromatography over silica gel using 10% chloroform in hexane as the eluent. Fractions containing only the title olefins as determined by TLC (silica gel; hexane) are combined to provide 11.7 g (71%) of the purified [E,Z] mixture of olefins in a ratio of 9 to 1, respectively.

H-NMR (300 mHz, CDCl3): δ 7.01-7.40 (3H, m), 5.67 (0.9H, q, J = 6.9 Hz), 5.53 (0.1H, q, J = 6.9 Hz), 2.41((1.8H, q, J = 7.6 Hz), 2.24 (0.2H, q, J = 7.6 Hz), 1.84 (2.7H, d, J = 7.6 Hz), 1.48 (0.3H, d, J = 7.6 Hz), 0.91 (2.7H, t, J = 7.6 Hz)), 0.86 (0.3H, t, J = 7.6 Hz)..

B. 3'-(4-hydroxy-3-methylphenyl)-3'-[3-chloro-4-(methylsulfonyloxy)-phenyl]pentane.



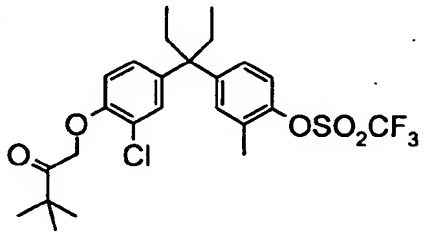
In a procedure analogous to Example 50D, [E,Z]-3-[3-chloro-4-(trifluoromethylsulfonyloxy)phenyl]-3-pentene (8.7 g, 26 mmol) and o-cresol (17.2 g, 159 mmol) in 200 mL methylene chloride are treated at RT with BF_3-etherate (1.47 g, 10.4 mmol) and the resulting mixture is stirred for 30 m at ambient temperature. The resulting light reddish brown solution is then worked up by the distillation and extraction procedure analogous to that used in the aforementioned example. The crude product was obtained as a tan oil which is purified by chromatography over silica gel with a gradient of 50% to 60% chloroform in hexane. Fractions that contained the desired product were combined and concentrated to provide the title compound as a pale tan oil (4.29g, 38%).

H-NMR (300 mHz, CDCl3): 6.5 to 7.3 (6H, m) 4.57 (1H,s), 2.21 (3H, s), 2.05 (4H, q, J = 7.3 Hz), 0.62 (6H, t, J =7.3 Hz).

ES(-) MS m/z: 435.1 (M-H); calc. 435.0645.

C. Preparation of 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)-phenyl]-3'-[3-methyl-4-(trifluoromethylsulfonyloxy)phenyl]pentane.

Note: (A Triflate Rearrangement Procedure)



In a procedure analogous to Example 50C, 3'-(3-chloro-4-hydroxyphenyl)-3'-[3-methyl-4-(methylsulfonyloxy)phenyl]pentane(4.00g, 9.17 mmol), 1-chloropinacolone (1.30 g, 9.62 mmol), anhydrous KI (76 mg, 0.46 mmol), and anhydrous K_2CO_3 (6.32 g, 45.9 mmol) are reacted in 125 mL acetonitrile. The title product is isolated and purified by silica gel chromatography using a gradient of 30% to 50% chloroform in hexane. Further chromatography of mixed fractions with a hexane to 10% EtOAc gradient provides additional pure compound (total amount 2.61 g, 53%).

H-NMR (300 mHz, CDCl3): δ 7.15 (1H, d, J = 2.3 Hz), 7.11 (1H, d, J= 8.4 Hz), 7.04 (1H, d, J = 2.3 Hz), 7.02 (1H, dd, J = 2.3 Hz, J = 8.4 Hz), 6.89 (1H, dd, J = 8.6 Hz, J = 2.3 Hz), 6.62 (1H, d, J = 8.6 Hz), 4.91 (2H, s), 2.32 (3H, s), 2.03 (4H, q, J = 7.2 Hz), 1.26 (9H, s), 0.60 (6H, t, J = 7.2 Hz).

ES(+) MS m/z: 552.2 (M+NH4); calc. 552.1798

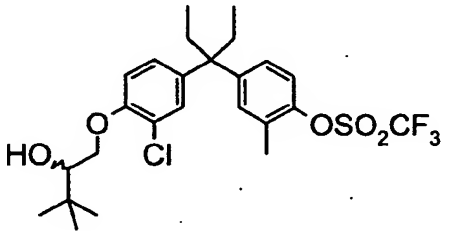
FAB(+) MS m/z [M]: 534.9; calc. 534.

Further NMR data: COSY data allowed the spin systems of the two aromatic rings to be grouped together. When the OCH2 was selectively excited, a NOE is observed with a resonance at 6.62 δ which is ortho only coupled. When the aromatic methyl (at 2.32 δ) was excited, a NOE is observed to a meta coupled proton at 7.04 δ. These resonances are not part of the same spin system, requiring the OCH2 and aromatic methyl to be on

different rings. Therefore the triflate has migtated during the reaction and the isolated product has the structure shown above. (HMBC data also supports this conclusion.)

Example 55

Preparation of racemic 3'-[3-chloro-4-(2-hydroxy-3.3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(trifluoromethylsulfonyloxy)phenyl]pentane.



In a procedure analogous to Example 51, 3'-[3-chloro-4-(2-oxo-3,3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(methylsulfonyloxy)phenyl]pentane (730 mg, 1.36 mmol) in 60 mL of MeOH is reduced by sodium borohydride (76 mg, 2.0 mmol). After 30 min, the mixture is quenched and worked up to provide the crude product which was purified by chromatography over silica gel with a gradient of hexane to 5% EtOAc in hexane to provide the title compound (719 mg, 98%)..

H-NMR (300 mHz, CDCl3): δ 7.15 (1H, d, J = 2.3 Hz), 7.13 (1H, d, J= 8.4 Hz), 7.05 (1H, d, J = 2.0 Hz), 7.03 (1H, dd, J = 2.3 Hz, J = 8.4 Hz), 6.96 (1H, dd, J = 8.6 Hz, J = 2.3 Hz), 6.86 (1H, d, J = 8.6 Hz), 4.20 (1H, dd, J = 8.9, 2.5 Hz), 3.906 (1H, t, J = 8.9 Hz), 3.75 (1H, dd, J = 8.9, 2.5 Hz), 2.59 (1H, br s), 2.34 (3H, s), 2.06 (4H, q, J = 7.3 Hz), 1.03 (9H, s), 0.63 (6H, t, J = 7.3 Hz).
ES(+) MS m/z: 554.2 (M+NH4); calc. 554.1954.
FAB(+) MS m/z [M]: 536.1; calc. 536.1661

Compounds of the Invention – Salts, Stereoisomers, & Prodrugs:

Salts of the compounds represented by formulae I are an additional aspect of the invention. The skilled artisan will also appreciate that the family of compounds of formulae I include acidic and basic members and that the present invention includes pharmaceutically acceptable salts thereof.

In those instances where the compounds of the invention possess acidic or basic functional groups various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, ammonium, calcium, magnesium, aluminum, zinc, and the like. Sodium and potassium saltgs are particularly preferred. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin. For example, a carboxylic acid substituent on the compound of Formula I may be selected as $-CO_2H$ and salts may be formed by reaction with appropriate bases (e.g., NaOH, KOH) to yield the corresponding sodium and potassium salt.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, choline, clavulanate, citrate, chloride, chloroprocaine, choline, diethanolamine, dihydrochloride, diphosphate, edetate, edisylate, estolate, esylate, ethylenediamine, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, bromide, chloride, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, malseate, mandelate, meglumine, mesylate, mesviate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pamoate, pantothenate, phosphate, polygalacturonate, procane, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or more chiral centers and may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of cis- and trans- isomeric forms of

the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a chiral column may be used such as those sold by Daicel Chemical Industries identified by the trademarks:
CHIRALPAK AD, CHIRALPAK AS, CHIRALPAK OD, CHIRALPAK OJ,
CHIRALPAK OA, CHIRALPAK OB, CHIRALPAK OC, CHIRALPAK OF,
CHIRALPAK OG, CHIRALPAK OK, and
CHIRALPAK CA-1.

By another conventional method, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers. These diastereomers, because they have different melting points, different boiling points, and different solubilities can be separated by conventional means, such as crystallization.

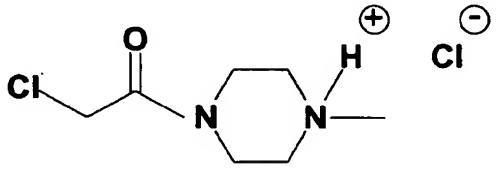
The present invention is also embodied in mixtures of compounds of formulae I .

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl

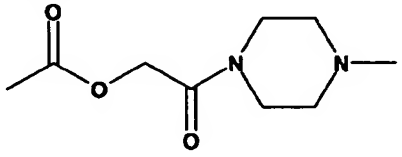
esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters to use as prodrugs are; methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, morpholinoethyl, and N,N-diethylglycolamido.

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No.25,099-6).

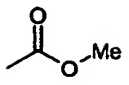
Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula I (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C5,220-3). For example, prodrugs may be prepared by reaction of the sodium salt for a compound of Formula I with;



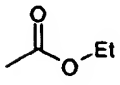
and sodium iodide to provide tthe ester prodrug pendent group



Also, lower alkyl (viz., C_1-C_8) ester prodrugs may be prepared by conventional means such as reacting the sodium or potassium salt (derived by forming the salt of any acidic compound of the invention; viz., reaction of a base such as KOH with an acidic group such as $-CO_2H$) of a compound of Formula I with an alkyl iodide such as methyl iodide, ethyl iodide, n-propyl iodide, isopropyl iodide. Typical ester prodrug substituents are



or



Pharmaceutical Formulations containing the Novel Compounds of the Invention:

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the compound of the invention (compounds of Formula I) together with a pharmaceutically acceptable carrier or diluent. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients.

In making the compositions of the present invention, the compounds of Formula I will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the compound. The compounds of the present invention are preferably formulated prior to administration.

The compounds of the invention may also be delivered by suitable formulations contained in a transderm patch. Alternatively, the compounds of the invention may be delived to a patient by sublingual administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example,

gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

In powders the carrier is a finely divided solid which is in admixture with the finely divided Active ingredient. In tablets the compound of Formula I is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the compound which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The Active Ingredient may be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The compounds can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided compounds of the invention in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Methods of Using the Compounds of the Invention:

Many disease states are benefited by treatment with the compounds of Formula I include, but are not limited to:

disease states characterized by abnormal calcium regulation
disease states characterized by abnormal cell proliferation
disease states characterized by abnormal cell differentiation
disease states characterized by abnormal immune response
disease states characterized by abnormal dermatological conditions
disease states characterized by neurodegenerative condition
disease states characterized by inflammation
disease states characterized by vitamin D sensitivity
disease states characterized by hyperproliferative disorders.

Specific disease states benefited by treatment of the compounds of Formula I and II include, but are not limited to:

Acne
Actinic keratosis
Alopecia
Alzheimer's disease
Bone maintenance in zero gravity
Bone fracture healing
Breast cancer
Chemoprovention of Cancer
Crohn's disease
Colon cancer
Type I diabetes
Host-graft rejection
Hypercalcemia
Type II diabetes
Leukemia
Multiple sclerosis
Myelodysplastic syndrome
Insufficient sebum secretion
Osteomalacia
Osteoporosis
Insufficient dermal firmness
Insufficient dermal hydration
Psoriatic arthritis
Prostate cancer
Psoriasis
Renal osteodystrophy
Rheumatoid arthritis
Scleroderma
Skin cancer
Systemic lupus erythematosus

Skin cell damage from Mustard vesicants

Ulcerative colitis

Vitiligo

Wrinkles

Particularly preferred is the treatment of psoriasis and osteoporosis by administration to a mammal (including a human) of a therapeutically effective amount of compounds of Formulae I. By "pharmaceutically effective amount" it is meant that quantity of pharmaceutical agent corresponding to formulae I which prevents, removes or reduces the deleterious effects of a disease state in mammals, including humans.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration and the condition being treated. Typical daily doses will contain a pharmaceutically effective amount typically in the range of from about 0.0001 mg/kg/day to about 50 mg/kg/day of body weight of an active compound of this invention. Preferably the dose of compounds of the invention will be from 0.0001 to 5 mg/kg/day of body weight.

Preferably compounds of the invention (e.g., per Formula I) or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active ingredient in a unit dose of composition may be varied or adjusted from about 0.0001 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it is necessary to make routine variations to the dosage depending on the age and condition of the patient. Dosage will also depend on the route of administration. The compounds of the inventiion may be administered by a variety of routes including oral, aerosol, rectal, transdermal, sublingual, subcutaneous, intravenous, intramuscular, and intranasal. Particularly preferred is the treatment of psoriasis with an ointment type formulation containing the compounds of the invention. The ointment formulation may be applied as needed, typically from one to 6 times daily.

Treatment of psoriasis is preferably done with topical application by a formulation in the form of a cream, oil, emulsion, paste or ointment containing a

therapeutically effective amount of a compound of the invention.. The formulation for topical treatment contains from 0.5 to 0.00005 weight percent, preferably from .05 to 0.0005 weight percent, and most preferably from 0.025 to 0.001 of a Active Ingredient.

For example, two semisolid topical preparations useful as vehicles for VDR modulators in treatment and prevention of psoriasis are as follows:

Polyethylene Glycol Ointment USP (p. 2495)

Prepare Polyethylene Glycol Ointment as follows:

Polyethylene Glycol 3350	400 g.
Polyethylene Glycol 400	600 g.
To make	1000 g.

Heat the two ingredients on a water bath to 65C. Allow to cool, and stir until congealed. If a firmer preparation is desired, replace up to 100 g of the polyethylene glycol 400 with an equal amount of polyethylene glycol 3350.

Hydrophilic Ointment USP (p. 1216)

Prepare Hydrophilic Ointment as follows:

Methylparaben	0.25 g.
Propylparaben	0.15 g.
Sodium Lauryl Sulfate	10 g.
Propylene Glycol	120 g.
Stearyl Alcohol	250 g.
White Petrolatum	250 g.
Purified Water	370 g.
To make about	1000 g.

The Stearyl Alcohol and White Petrolatum are melted on a steam bath, and warmed to about 75C. The other ingredients, previously dissolved in the water are added, warmed to 75C, and the mixture stirred until it congeals.

For each of the above formulations the Active Ingredient is added during the heating step in an amount that is from 0.5 to 0.00005 weight percent, preferably from .05 to 0.0005 weight percent, and most preferably from 0.025 to 0.001 weight percent of the total ointment weight. (Source: - United States Pharmacopoeia 24, United States Pharmacopeial Convention, 1999)

Conventional therapy for osteoporosis includes; (i) estrogens, (ii) androgens, (iii) calcium supplements, (iv) vitamin D metabolites, (v) thiazide diuretics, (vi) calcitonin, (vii) bisphosphonates, (viii) SERMS, and (ix) fluorides (see, Harrison's Principles of Internal Medicine, 13th edition, 1994, published by McGraw Hill Publ., ISBN 0-07-032370-4, pgs.2172-77; the disclosure of which is incorporated herein by reference.). Any one or combination of these conventional therapies may be used in combination with the method of treatment using compounds of Formulae I as taught herein. For example, in a method of treating osteoporosis, the vitamin D receptor modulator compounds of the invention (e.g., as defined by formula I) may be administered separately or simultaneously with a conventional therapy. Alternatively, the vitamin D receptor modulator compounds of the invention may be combined with conventional therapeutic agents in a formulation for treatment of osteoporosis such as set out below:

A formulation for treating osteoporosis comprising:

Ingredient (A1): a vitamin D receptor modulator represented by formula (I), or a pharmaceutically acceptable salt or prodrug derivative thereof;

Ingredient (B1):

one or more co-agents that are conventional for treatment osteoporosis selected from the group consisting of:

a. estrogens,
b. androgens,
c. calcium supplements,
d. vitamin D metabolites,
e. thiazide diuretics,
f. calcitonin,
g. bisphosphonates,
h. SERMS, and
i. fluorides.

Ingredient (C1): optionally, a carrier or diluent.

Typically useful formulations are those wherein the weight ratio of (A1) to (B1) is from 10:1 to 1:1000 and preferably from 1:1 to 1:100.

Combination Therapy for Psoriasis:

Conventional therapy for psoriasis includes topical glucocorticoids, salicylic acid, crude coal tar, ultraviolet light, and methotrexate (see, Harrison's Principles of Internal Medicine, 13th edition, 1994, published by McGraw Hill Publ., ISBN 0-07-032370-4, pgs.2172-77). Any one or combination of these conventional therapies may be used in combination with the method of treatment using compounds of Formulae I as taught herein. For example, in a method of treating osteoporosis, the vitamin D receptor modulator compounds of the invention (e.g., as defined by formula I) may be topically administered separately or simultaneously with a conventional therapy. Alternatively, the vitamin D receptor modulator compounds of the invention may be combined with conventional therapeutic agents in a topically applied formulation for treatment of osteoporosis such as set out below:

A formulation for treating psoriasis comprising:

Ingredient (A2): a vitamin D receptor modulator represented by formula (I), or a pharmaceutically acceptable salt or prodrug derivative thereof;

Ingredient (B2):

one or more co-agents that are conventional for treatment psoriasis selected from the group consisting of:

a. topical glucocorticoids ,

b. salicylic acid, or

c. crude coal tar.

Ingredient (C2): optionally, a carrier or diluent.

Typically useful formulations are those wherein the weight ratio of (A2) to (B2) is from 1:10 to 1:100000 and preferably from 1:100 to 1:10000.

Assays and Test Results:

Table 3

Summary of Experimental Results

Test Cmpd. [1]	RXR-VDR heterodime	VDR EC_{50} (nM)	OCN Promoter [4]	Mouse Hypercal [5]

	r^2 EC_{50} (nM)	(Caco-2 cells)[3]	EC_{50} (nM)	µg/Kg/d
Ex. 1	3.41	117.81	2.72	
Ex. 2		46.5	5.1	50
Ex. 3		133	16.3	50
Ex. 4		164	0.91	
Ex. 5		1594.5	20.75	>500
Ex. 6		1138	11.3	300
Ex. 7		331	84	100
Ex. 8		34.75	3.48	
Ex. 9		13		
Ex. 10		15	0.3	
Ex. 12		112	2.325	
Ex. 14		89	9.77	<300
Ex. 17			3.75	
Ex. 18	69.56	485.21	7.625	1500

Ex. 19			16.75	
Ex. 20			28.1	500
Ex. 21			124.5	
Ex. 22			29.8	500
Ex. 23	0.817	6.0645	0.33	500
Ex. 24			44.65	<1000
Ex. 25	47.26	1285.266	34.25	
Ex. 26	5.697	333.00	3.685	<1000
Ex. 27			10.59	500
Ex. 28			17.9	1000
Ex. 29			4.585	100
Ex. 30			103.8	
Ex. 31			44	
Ex. 32			239.57	
Ex. 33			49.37	
Ex. 34			373.53	

Ex. 35	137.92	615.60	20.1	
Ex. 36 2044283	15.226	592.38	45.5	>3000
Ex. 37		308.25	67.23	
Ex. 38			2.085	<300
Ex. 39		18	1.79	<100
Ex. 40		374.5	1.905	300
Ex. 41		614	111.4	
Ex. 42	495.3014	728.4	25.15	<1000
Ex. 43,51			7.525	
Ex. 44	2.208	86.604	2.4	
Ex. 45,51B	24.00	353.18	13	
Ex. 48			54.1	<1000
Ex 46 ,52			217.1	
Ex. 47,53	12.53	430.90	92.45	
AA	12	16	5	0.06
BB		225	11	20

CC		710000	10000	>30000

Table 4

Summary of Experimental Results

Test Cmpd. [1]	Kera. Prolif. IC_{50} (nM)	IL-10 IC_{50} (nM)
Ex. 14	2	
Ex. 17	2	
Ex. 18	32	
Ex. 21	67	
Ex. 25	14.55	
Ex. 26	4.4	
Ex. 36	36	
Ex. 42	9	
Ex. 43,51	4	
Ex. 45,51B	27	39.5087
Ex 46 ,52	90	
Ex. 47,53	300	
Ex. 48	13	

AE	18	

Explanation of Table 3 and 4 column numerical superscripts:

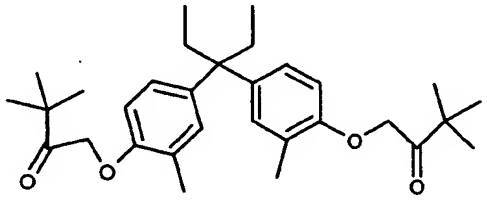
1. Test Compound coded with Example numbers correspond to the products of the same numbered example in the specification. Alphbetical symbols (e.g., "AA", "BZ") correspond to the chemical species identified by the same symbol in the specificaton.

"AA" = 1α,25-dihydroxyvitamin D_3

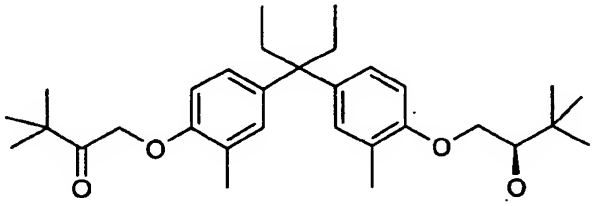
"BB" = 3-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-phenoxy)-propane-1,2-diol

"CC" = 1-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-cyclohexyl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-one

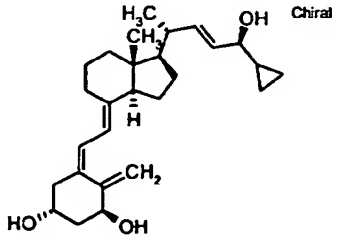
"DD" = compound represented by the formula:



"EE" = compound represented by the formula:



"FF" = calcipotriol (structural formula below):



2. The RXR-VDR heterodimerization (SaOS-2 cells) test is described in the "Assay" section of the Description, infra.

3. The VDR CTF (Caco-2 cells) test is described in the "Assay" section of the Description, infra.

4. The OCN Promoter test is described in the "Assay" section of the Description, infra.

5. The Mouse Hypercalcemia test is described in the "Assay" section of the Description, infra.

6. The keratinocyte proliferation assay is described in the "Assay" section of the Description, infra.

7. The IL-10 induction assay is described in the "Assay" section of the Description, infra.

Assay Methods

Use of the Assay Methods:

The evaluation of the novel compounds of the invention for osteoporosis and other related diseases is done using a plurality of test results. The use of multiple assays is necessary since the combined properties of (i) high activity for the vitamin D receptor, and (ii) prevention of hypercalcemia must be achieved to have utility for the methods of treating diseases, which are also, aspects of this invention. Some of the tests described below are believed related to other tests and measure related properties of compounds. Consequently, a compound may be considered to have utility in the practice of the invention if is meets most, if not all, of the acceptance criteria for the above described tests.

The evaluation of the novel compounds of the invention for psoriasis is done using the Keratinocyte Proliferation Assay in combination with other assays that measure inhibition of IL-2 production and stimulation of IL-10 production in peripheral blood mononuclear cells (PBMCs).

Brief Description, Utility and Acceptance Criteria for the Assay Methods:

1. The RXR-VDR heterodimerAssay:

This assay provides the VDR activity of a test compound. It is

desirable to have low EC50 values for a compound in this assay. The lower the EC50 value, the more active the compound will be as a VDR agonist. Desired assay results are EC50 values less than or equal to 600 nM. Preferred assay results are less than 250 nM, and most preferably less than 150 nM.

2. The Caco-2 cell Co-transfection Assay:

The Caco-2 cell assay is an indicator for the undesirable condition of hypercalcemia. This co-transfection assay is a surrogate assay for in vivo calcemic activity of VDR ligands. It is desirable to have high EC50 values for a test compound in this assay. The higher the EC50 values for a compound the less calcemic it will be in vivo. Desired assay results are EC50 greater than or equal to 300 nM. Preferred assay results are greater than 1000 nM.

3. The OCN (osteocalcin) Promoter Assay

The OCN Promoter Assay is an indicator and marker for osteoporosis. Desired assay results are EC50 less than or equal to 325 nM. Preferred assay results are less than 50 nM.

4. The Mouse Hypercalcemia Assay

The Mouse Hypercalcemia Assay is a six day hypercalcemia test for toxicity and selectivity. Acceptable test results are levels greater than 300 μg/kg/day. Preferred assay results are levels greater than 1000 μg/kg/day.

5. The Keratinocyte Proliferation Assay

This Assay is indicative for the treatment of psoriasis. An acceptable test result is IC50 value of less than or equal to 300 nM. Preferred assay results are IC50 values of less than 100 nM.

6. The IL-10 induction Assay

This is an in vitro efficacy assay for psoriasis, abscess and adhesion. Psoriasis involves both keratinocytes and immune cells. IL-10 is a unique cytokine because it is anti-inflammatory and immunosuppressive. This assay tells us whether a VDRM is able to

function as an agonist in PBMCs (primary blood mononuclear cells) or not. A lower EC50 value is desirable in this assay since a compound with a lower EC50 value will be a better agonist in PBMCs. An acceptable test result is an EC50 value of less than 200 nM. Preferred assay results are EC50 values of less than 100 nM.

7. Other Compound Assay Standards

An alternative measusre of the efficacy of compounds of the invention for treatment of osteoporosis is a numerical ratio calculated as follows:

Dose Threshold needed to induce hypercalcemia

divided by

Dose Threshold needed for bone efficacy

An alternative measusre of the efficacy of compounds of the invention for treatment of psoriasis is a numerical ratio calculated as follows:

Dose Threshold needed to induce hypercalcemia

divided by

Dose Threshold needed to induce keratinocyte proliferation

For the above ratios, Dose Thresholds are determined from dose response curve data.

Details of the Assay Methods:

(1) Materials and Method for RXR-VDR Heterodimerization Assay:

Transfection Method:

- FuGENE 6 Transfection Reagent (Roche Cat # 1 814 443)

Growth Media:

- D-MEM High Glucose (Gibco BRL Cat # 11054-020), 10% FBS, 1% antibiotic-antimycotic (Ab-Am)

FBS heat inactivated (Gibco BRL Cat # 10092-147)

Ab-Am (Gibco BRL Cat # 15240-062)

Cells:

- Grow SaOs-2 cells in T-152 cm^2 culture flasks in *growth media*.
- Keep the density at 5-6 x 10^5 cells/ml
- Passage cells 1:3 twice a week

- Add Trypsin EDTA (Gibco BRL Cat # 25300-020)and incubate
- Resuspend cells in plating media and transfer into growth media.

Wash Media:

- HBSS Low Glucose Without Phenol Red (Gibco BRL Cat # 14175-095), 1% Ab-Am

Plating Media:

- D-MEM Low Glucose Without Phenol Red (Gibco BRL Cat # 11054-020), 1% Ab-Am

D-MEM

Stripped FBS (Hyclone Cat# SH30068.03 Lot # AHM9371)

Ab-Am

Transfection / Treatment Media:

- D-MEM Low Glucose Without Phenol Red only

T-152 cm^2 culture flask:

- Use Corning Coastar T-152 cm^2 culture flask (Cat # 430825) to grow the cells

Flat well Plates:

- Use well plate to plate cells
- Use Deep well plate sterile to make up treatment media.

Luciferase Assay Reagent:

- Use Steady-Glo Luciferase Reagent from Promega (Cat # E2550) Consists of:

a. E2533 Assay Substrate, lyopholized product and

b. E2543 Assay Buffer.

- Thaw at room temperature
- Store

DAY 1: Cell Plating:

Cell Harvesting

Aspirate media from culture flask, rinse cells with HBSS and aspirate.

Add trypsin and incubate.

When cells appear detached, resuspend cells in *growth media.*

Transfer into a new flask with fresh *growth media* for passaging the cells.

Plate well plates and two extra plates

A. Cell Count

Mix the cell suspension using pipette

Use *Hematocytometer* to count the cells

Load cell suspension onto the hemocytometer chamber

Count cells.

Plate seeding:

Use plating media 10 % Stripped FBS in D-MEM Low Glucose, Without Phenol Red, 1% Ab-Am

Plate 14 plates @ 165 µl / well.

In sterile flask add cell suspension

to *plating media.*

Mix .

Add cells / well.

Place the cells in the incubator.

Cells should be about 75 % confluent prior to transfection.

Step 1: DNA and Media

Add plain DMEM media to tubes for mixing the DNA

Add the Reporter gene pFR-LUC

Add the Gal4-RXR-DEF and VP16-VDR-LBD

Step 2: FuGENE and Media

Prepare plain DMEM media in a ubes for mixing FuGENE

Add *FuGENE 6 Transfection Reagent*

Incubate

Step 3: FuGENE , DNA and Media Complex

Add FuGENE Media complex from step 2 to DNA Media complex from step1

Incubate

Step 4: FuGENE , DNA and Media Complex to-well plate

Add FuGENE-DNA-Media complex from step 3 to each plate

Incubate.

Day 3: Dosing

Treatment preparation

Allow for transfection time

Make a stock solution of the compounds in DMSO

Vortex until all the compounds has been dissolved.

Further dilute in D-MEM (Low Glucose – With out Phenol Red)

Add compounds in quadruplicate to give final volume

Incubate.

Day 4: Luciferase Assay

Read the plates after drug treatment

Remove part of media from all the wells and leave remainder

Add Steady-Glo Luciferase Reagent mixture / wells

Incubate

Count each well using a Luminescence counter, Top Count NXT by Packard

Set a delay between plates to reduce the background.

(2) Materials and Method for The Caco-2 Cell Assay:

Caco-2 cells, grown in phenol red free, DMEM (Invitrogen, Carlsbad, CA) containing 10 % charcoal-stripped FCS (Hyclone, Logan, UT), were transfected with Fugene 6 reagent (Roche Diagnostics, Indianapolis, IN). Cells (5000/well) were plated 18 h before transfection in a 96 well plate. The Cells were transfected with Gal4-responsive reporter pFRLuc (150 ng, Stratagene, La Jolla CA) and the receptor expression vector pGal4-VDR-LBD (10 ng), along with Fugene 6 reagent (0.2 µl/well). The DNA-Fugene complex was formed by incubating the mixture for 30 min at room temperature. The cells were transfected in triplicate for 5 h, and treated with various concentrations of VDR ligands (form 0.01 nM to 10,000 nM concentration range) 18h post-transfection. The luciferase activity was quantified using Steady-Glo reagent kit (Promega, Madison, WI) as per manufacturer's specifications.

(3) Materials and Method for The OCN Promoter Assay:

The activation of osteocalcin by VDR ligands was evaluated in a rat osteoblast-like cell line RG-15 (ROS 17/2.8) stably expressing rat osteocalcin promoter fused with luciferase reporter gene. The stable cell lines were established as reported before (Activation of Osteocalcin Transcription involves interaction of protein kinase A- and Protein kinase C-dependent pathways. Boguslawski, G., Hale, L. V., Yu, X.-P., Miles, R. R., Onyia, J. E., Santerre R. F., Chandrasekhar, S. J Biol. Chem. 275, 999-1006, 2000). Confluent RG-15 cells maintained in DMEM/F-12 medium (3:1) containing 5% FBS, 300 □g/ml G418 and at 37°C under 5% CO_2/95% air atmosphere were trypsinized (0.25% trypsin) and plated into white opaque 96-well cell culture plates (25000 cells/well). After 24 hr, cells (in DMEM/F-12 medium + 2% FBS) were treated with various concentrations of compounds, dissolved in DMSO. The final DMSO concentration remained at 0.01% (v/v). After 48 hr treatment, the medium was removed, cells were lysed with 50 □l of lysis buffer (From Luciferase reporter assay system, Roche Diagnostics, Indianapolis, IN) and assayed for luciferase activity using the Luciferase Reporter Gene Assay kit from Boehringer Mannheim as per manufacturer's specifications.

(4) Materials and Method for The Mouse Hypercalcemia Assay:

Weanling, virus -antibody-free, five to six weeks old female DBF mice (Harlan, Indianapolis, IN) are used for all the studies. Animals are allowed to acclimate to local vivarium conditions for 2 days. Mice are maintained on a 12 hr light/dark cycle at 22°C with ad lib access to food (TD 5001 with 1.2% Ca and 0.9%P, Teklad, Madison, WI) and water. The animals then are divided into groups with 4-5 mice per group. Different doses of test compounds prepared in 10% Ethanol and 90% sesame oil are administered to mice orally via gavage for 6 days. 1α-25$(OH)_2D_3$ 0.5μg/kg/d was also given to one group of mice as the positive control. Serum ionized calcium is evaluated at 6 hours after the last dosing under isoflurane anesthesia by Ciba-Corning Ca++/PH Analyzer, (Model 634, Chiron Diagnostics Corp., East Walpole, MA). Raw data of group differences is assessed by analysis of variance (ANOVA) using Fisher's protected least significant difference (PLSD) where the significance level was $P< 0.05$.

(5) The Keratinocyte Proliferation Assay:

KERtr cells (Human skin keratinocyte transformed with a retrovirus vector, obtained from ATCC) were plated in 96-well flat-bottomed plates (3000 cells/well) in 100 □l keratinocyte serum free medium supplemented with bovine pituitary extract in the absence of EGF (Life Technologies, Rockville, MD) and incubated at 37°C for two days. The cells were treated with various concentrations of VDR ligands (ten-fold serial dilution from 10,000 nM to 0.1 nM in triplicate), dissolved in 100 □l keratinocyte serum free medium supplemented with bovine pituitary extract in the absence of EGF and incubated at 37°C for 72hr. BrdU (5-bromo-2'-deoxyuridine) incorporation was analyzed as a measure of DNA replication (Cell proliferation ELISA kit, Roche Diagnostics, Indianapolis, IN) and absorbance was measured at 405 nm. Potency values (IC_{50}) values were determined as the concentration (nM) of compound that elicited a half-maximal response.

(6) Materials and Method for human IL-10 Induction Assay:

Isolation of peripheral blood mononuclear cells (PBMCs):

A. Collect 50 ml of human blood and dilute with media, RPMI-1640.

B. Prepare sterile tubes with ficol.

C. Add diluted blood to tubes.

D. Centrifuge.

E. Discard the top layer and collect the cells from middle layer.

F. Divide all cells into four tubes and add media.

G. Centrifuge.

H. Aspirate off media and resuspend.

I. Collect all cells

J. Centrifuge. at 1200 rpm for 10 minutes.

K. Resuspend in RPMI-1640 with 2% FBS and count cells

Stimulation of PBMC:

L. Prepare TPA in DMSO.

M. Dissolve PHA in water .

N. Plate TPA/PHA treated PBMCs in well plates.

O. Incubate.

Treatment:

P. Prepare all compound dilutions in plain RPMI- 1640 media.

Q. Add diluted compound.

R. Incubate.

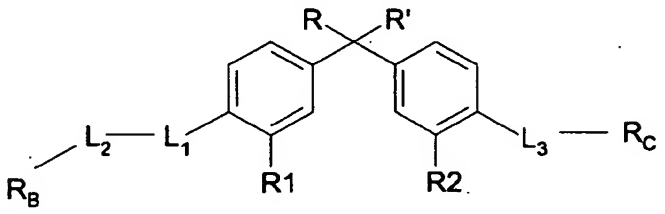
Sample Collection and assay:

S. Remove all the cells by centrifugation and assay the supernatant for IL-10 by immunoassay.

1) T. Perform IL-10 assay using anti-human IL-10 antibody coated beads, as described by the manufacturer (Linco Research Inc., St. Charles, MO).

WE CLAIM:

1. A compound represented by formula (I) or a pharmaceutically acceptable salt or a prodrug derivative thereof:



(I)

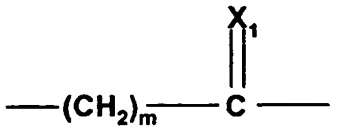
wherein;

R and R' are independently C_1-C_5 alkyl, C_1-C_5 fluoroalkyl, or together R and R' form a substituted or unsubstituted, saturated or unsaturated carbocyclic ring having from 3 to 8 carbon atoms;

R1 and R2 are independently selected from the group consisting of hydrogen, halo, C_1-C_5 alkyl, C_1-C_5 fluoroalkyl, -O-C_1-C_5 alkyl, -S-C_1-C_5 alkyl, -O-C_1-C_5 fluoroalkyl, -CN, -NO_2, acetyl, -S-C_1-C_5 fluoroalkyl, C_2-C_5 alkenyl, C_3-C_5 cycloalkyl, and C_3-C_5 cycloalkenyl;

L_1 and L_2 and L_3 are independently divalent linking groups independently selected from the group consisting of

a bond ,



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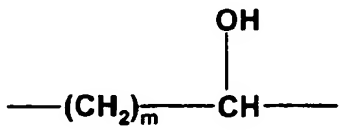

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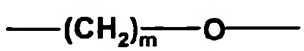

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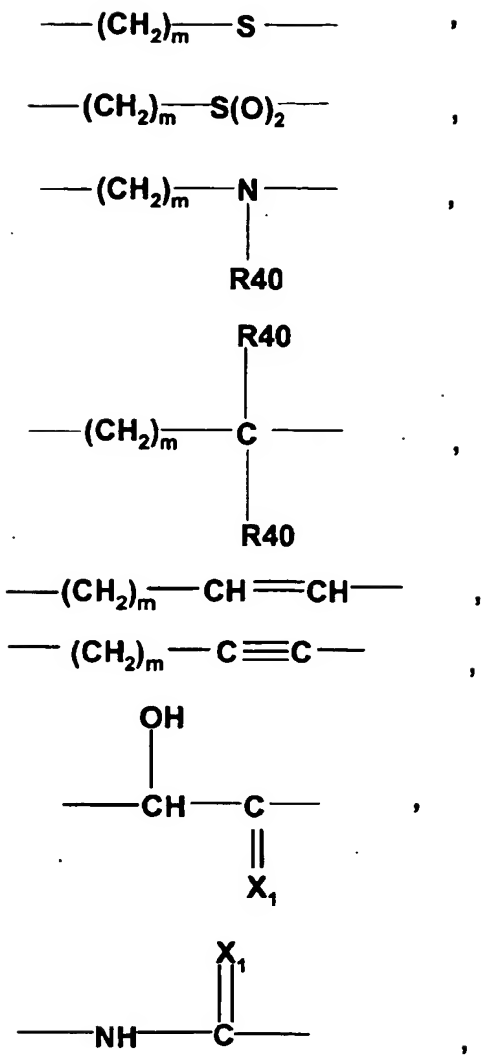


where m is 0, 1 or 2, X_1 is oxygen or sulfur, and each R40 is independently hydrogen, C_1-C_5 alkyl, or C_1-C_5 fluoroalkyl;

R_B is

branched C_3-C_5 alkyl,

3-methyl-3-hydroxypentyl,

3-methyl-3-hydroxypentenyl,

3-methyl-3-hydroxypentynyl,

3-ethyl-3-hydroxypentyl,

3-ethyl-3-hydroxypentenyl,

3-ethyl-3-hydroxypentynyl,

3-ethyl-3-hydroxy-4-methylpentyl,

3-ethyl-3-hydroxy-4-methylpentenyl,
3-ethyl-3-hydroxy-4-methylpentynyl,
3-propyl-3-hydroxypentyl,
3-propyl-3-hydroxypentenyl,
3-propyl-3-hydroxypentynyl,
1-hydroxy-2-methyl-1-(methylethyl)propyl,
3-methyl-3-hydroxy-4,4-dimethylpentyl,
3-methyl-3-hydroxy-4,4-dimethylpentenyl,
3-methyl-3-hydroxy-4,4-dimethylpentyl,
3-ethyl-3-hydroxy-4,4-dimethylpentynyl,
3-ethyl-3-hydroxy-4,4-dimethylpentenyl,
3-ethyl-3-hydroxy-4,4-dimethylpentynyl,
4,4-dimethyl-3-hydroxypropyl,
1-hydroxycyclopentenyl,
1-hydroxycyclohexenyl,
1-hydroxycycloheptenyl,
1-hydroxycyclooctenyl,
1-hydroxycyclopropyl,
1-hydroxycyclobutyl,
1-hydroxycyclopentyl,
1-hydroxycyclohexyl,
1-hydroxycycloheptyl, or
1-hydroxycyclooctyl;

provided, however, that when

R_B is

3-methyl-3-hydroxypentyl,
3-methyl-3-hydroxypentenyl,
3-methyl-3-hydroxypentynyl,
3-ethyl-3-hydroxypentyl,
3-ethyl-3-hydroxypentenyl,
3-ethyl-3-hydroxypentynyl,
4,4-dimethyl-3-hydroxypropyl,

3-ethyl-3-hydroxy-4-methylpentyl,
3-ethyl-3-hydroxy-4-methylpentenyl,
3-ethyl-3-hydroxy-4-methylpentynyl,
3-propyl-3-hydroxypentyl,
3-propyl-3-hydroxypentenyl,
3-propyl-3-hydroxypentynyl,
3-methyl-3-hydroxy-4,4-dimethylpentyl,
3-methyl-3-hydroxy-4,4-dimethylpentenyl,
3-methyl-3-hydroxy-4,4-dimethylpentyl,
3-ethyl-3-hydroxy-4,4-dimethylpentynyl,
3-ethyl-3-hydroxy-4,4-dimethylpentenyl,
3-ethyl-3-hydroxy-4,4-dimethylpentynyl, or
1-hydroxy-2-methyl-1-(methylethyl)propyl;

then L_1 and L_2 combine as a bond; and

R_C is

-O-SO_2-(R50)

where R50 is

-C_{1-3}alkyl, -CF_3, -$(CH_2)_{1-2}CF_3$,
-S-C_{1-3}alkyl , -SO_2-C_{1-3}alkyl,
-$(CH_2)_{1-2}$C(O)NHMe,
-$(CH_2)_{1-2}$-CO_2H; or

-NH-SO_2-(R50)

where R50 is

-C_{1-3}alkyl, -CF_3, -$(CH_2)_{1-2}CF_3$,
-S-C_{1-3}alkyl , -SO_2-C_{1-3}alkyl,
-$(CH_2)_{1-2}$-CO_2H,
-$(CH_2)_{1-2}$C(O)NHMe, or

$-N(SO_2R51)_2$

where each R51 is independently,

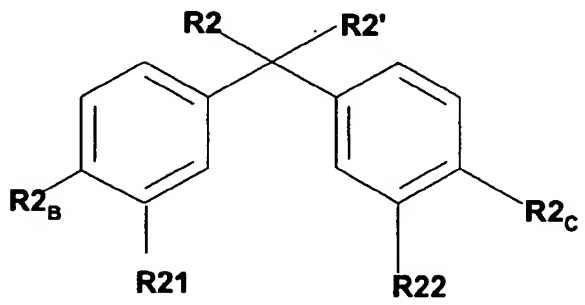
$-C_{1-3}$alkyl, $-CF_3$, $-(CH_2)_{1-2}CF_3$,

$-(CH_2)_{1-2}C(O)NHMe$,

$-S-C_{1-3}$alkyl , $-SO_2-C_{1-3}$alkyl, or

$-(CH_2)_{1-2}-CO_2H$.

2. A compound represented by formula (II) or a pharmaceutically acceptable salt or a prodrug derivative thereof:



(II)

wherein;

R2 and R2' are independently methyl or ethyl;

R21 and R22 are independently selected from the group consisting of hydrogen, fluoro, -Cl, $-CF_3$, $-CH_2F$, $-CHF_2$, methoxy, ethoxy, vinyl, methyl, ethyl, propyl, 1-methylethyl, 1,1-dimethylethyl, butyl, 1-methylpropyl, 2-methylpropyl, or cyclopropyl;

$R2_B$ is a group represented by the formula:

3-methyl-3-hydroxypentyl,

3-methyl-3-hydroxypentenyl,

3-methyl-3-hydroxypentynyl,

3-ethyl-3-hydroxypentyl,

3-ethyl-3-hydroxypentenyl,

3-ethyl-3-hydroxypentynyl,

3-ethyl-3-hydroxy-4-methylpentyl,

3-ethyl-3-hydroxy-4-methylpentenyl,

3-ethyl-3-hydroxy-4-methylpentynyl,

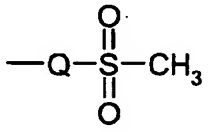
3-propyl-3-hydroxypentyl,

3-propyl-3-hydroxypentenyl,

3-propyl-3-hydroxypentynyl,

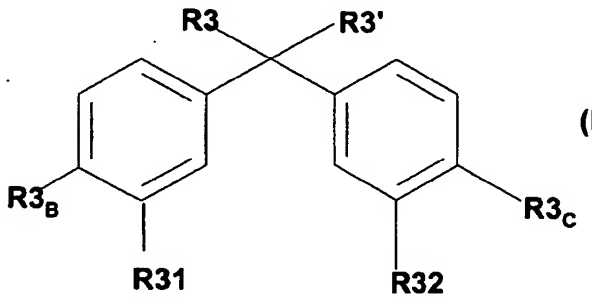
1-hydroxy-2-methyl-1-(methylethyl)propyl

$R2_C$ is



where Q is –O- or –NH-.

3. A compound represented by formula (III) or a pharmaceutically acceptable salt or a prodrug derivative thereof:



(III)

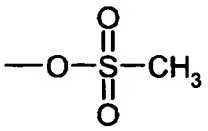
wherein;

R3 and R3' are independently methyl or ethyl;

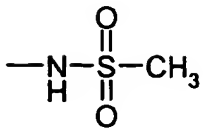
R31 and R32 are independently selected from the group consisting of hydrogen, fluoro, -Cl, $-CF_3$, $-CH_2F$, $-CHF_2$, methoxy, ethoxy, vinyl, methyl, ethyl, propyl, 1-methylethyl, 1,1-dimethylethyl, butyl, 1-methylpropyl, 2-methylpropyl, or cyclopropyl;

$R3_B$ is 3-hydroxy-3-ethyl-pentyl or 4,4-dimethyl(-3-hydroxypropyl).

$R3_C$ is

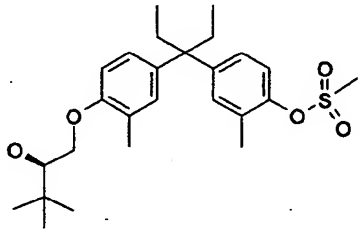


or

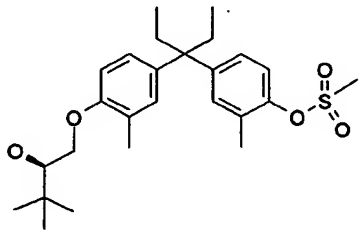


4. A compound or a pharmaceutically acceptable salts or an ester prodrug derivative thereof represented by the structural formulae M-1 to M-31 as follows:

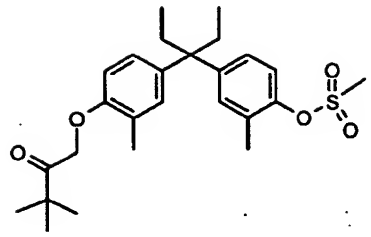
M-1)



M-2)



M-3)



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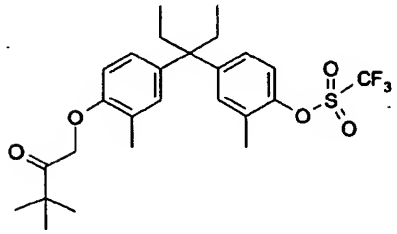
M-4)



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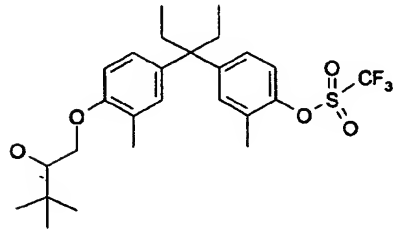
M-5)



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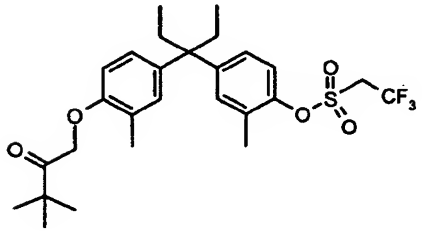
M-6)



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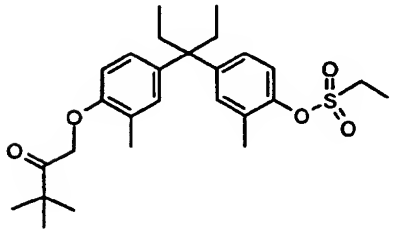
M-7)



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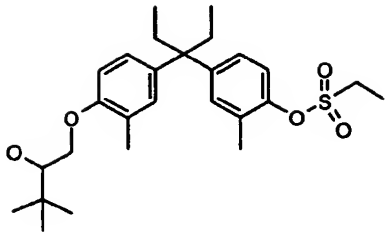
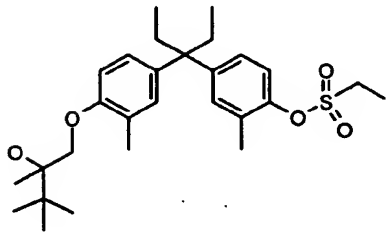
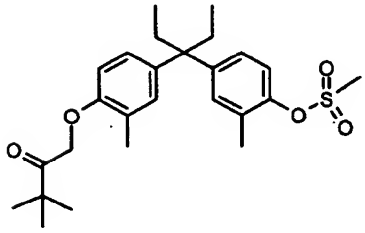
M-8)



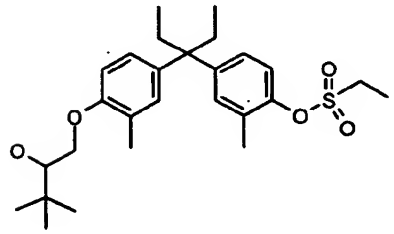
M-9)



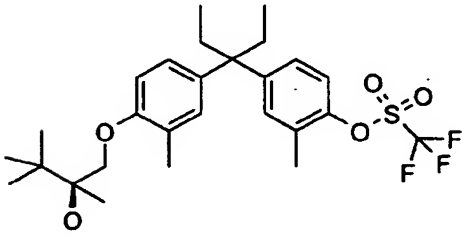
M-10)



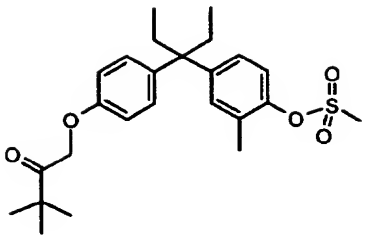
M-11)



M-12)



M-13)



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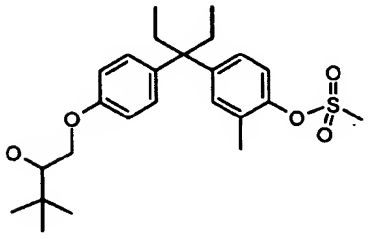
M-14)



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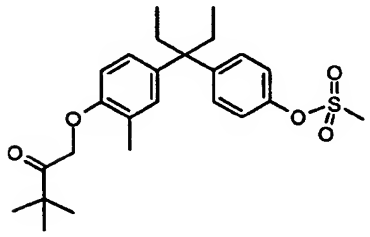
M-15)



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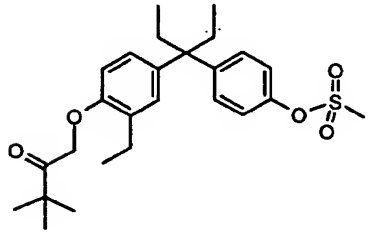
M-16)



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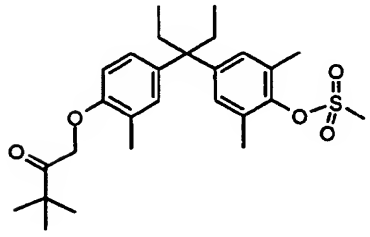
M-17)



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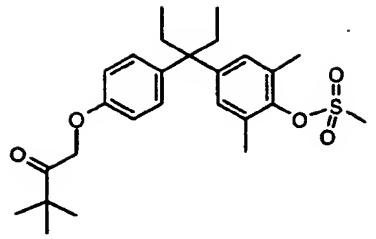
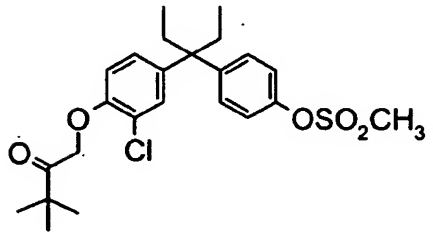
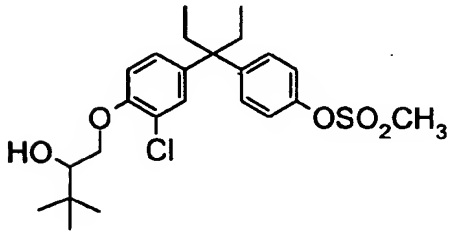
M-18)



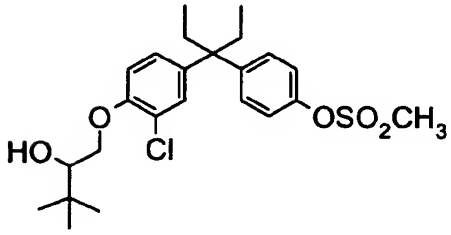
M-19)



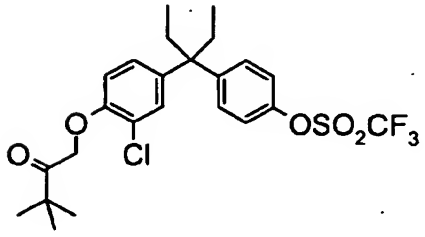
M-20)



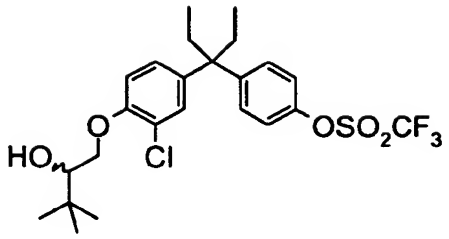
M21)



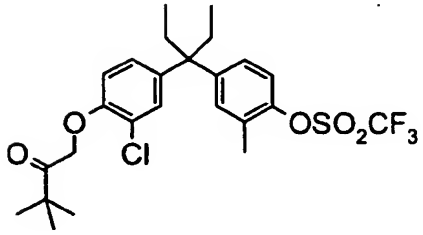
M-22)



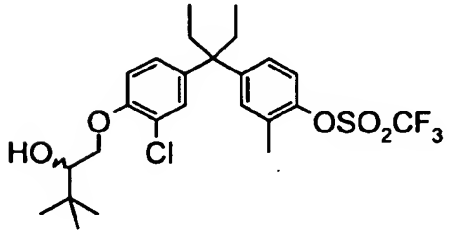
M-23)



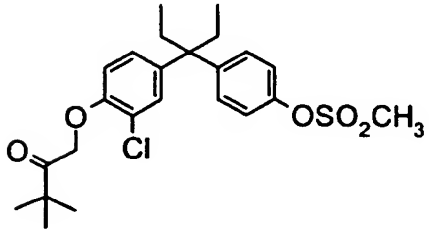
M-24)



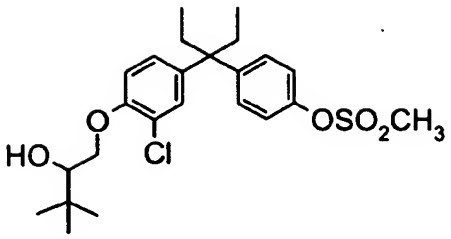
M-25)



M-26)



M-27)



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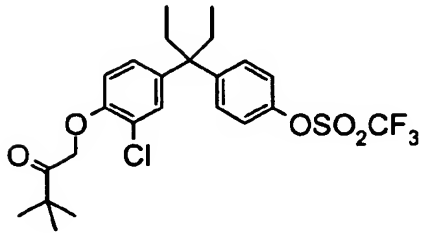
M-28)



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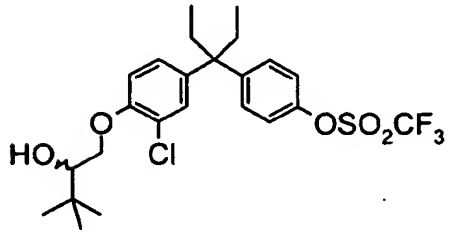
M-29)



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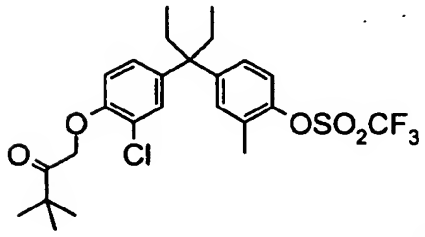
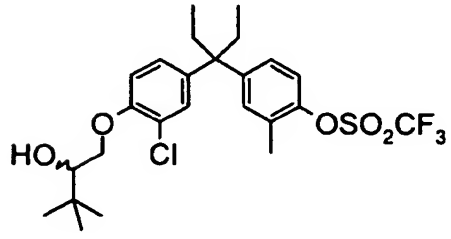
M-30)



or

M-31)



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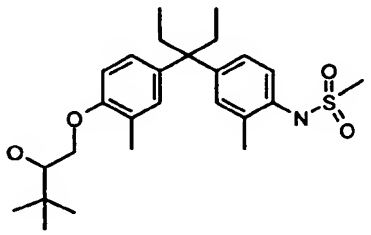
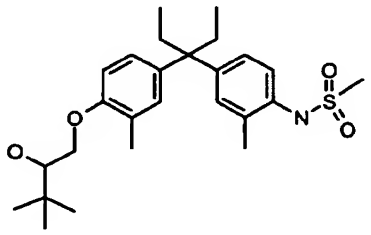
5. A compound or a pharmaceutically acceptable salts or an ester prodrug derivative thereof represented by the structural formulae M-1 to M-31 as follows:

derivatives are represented by the structural formulae M-32 to M-50 as follows:

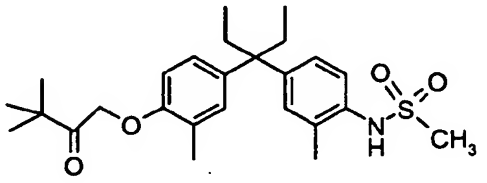
M-32)



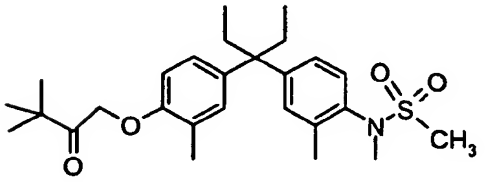
M-33)



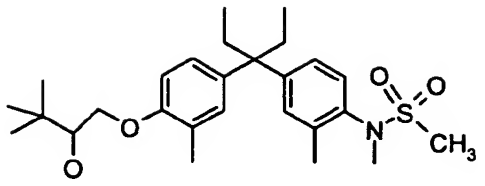
M-34)



M-35)



M-36)



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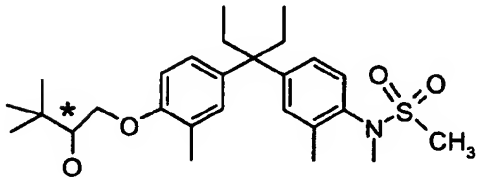
M-37)



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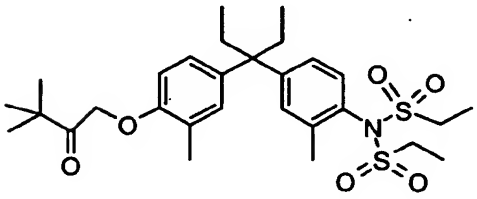
M-38)



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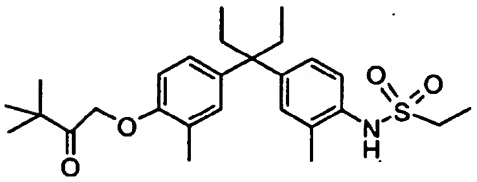
M-39)



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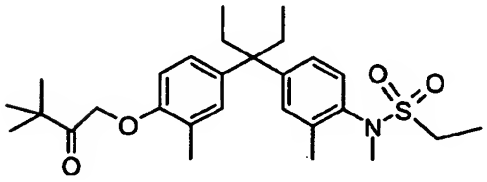
M-40)



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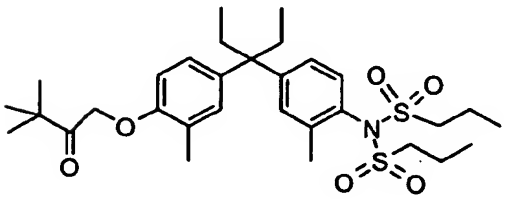
M-41)



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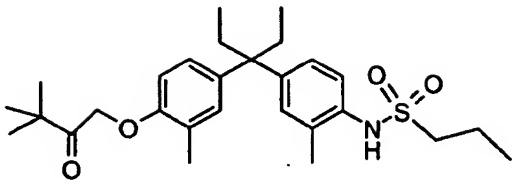
M-42)



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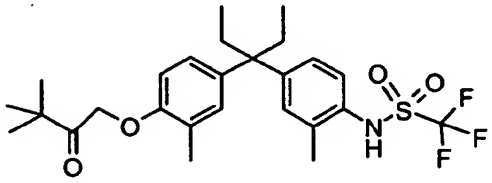
M-43)



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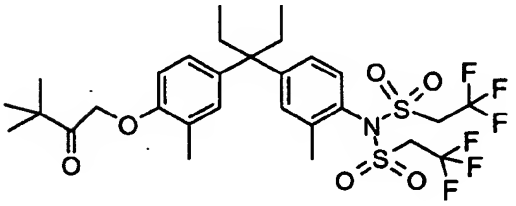
M-44)



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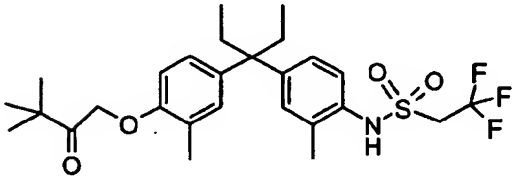
M-45)



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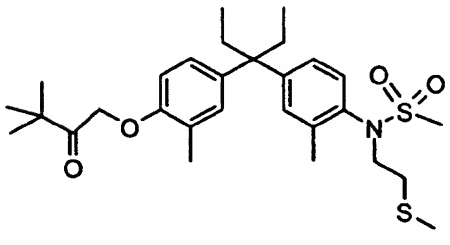
M-46)



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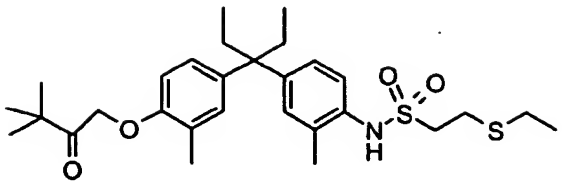
M-47)



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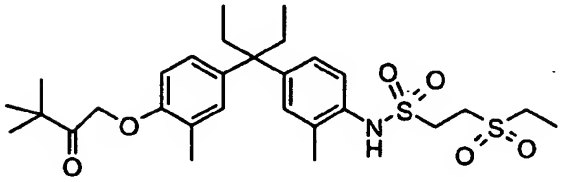
M-48)



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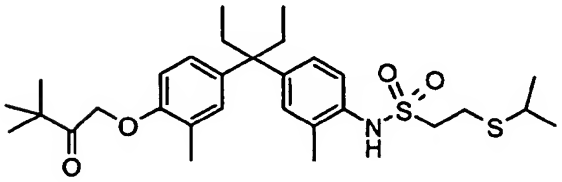
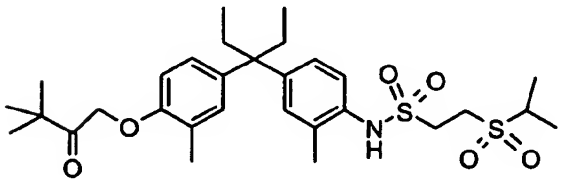
M-49)

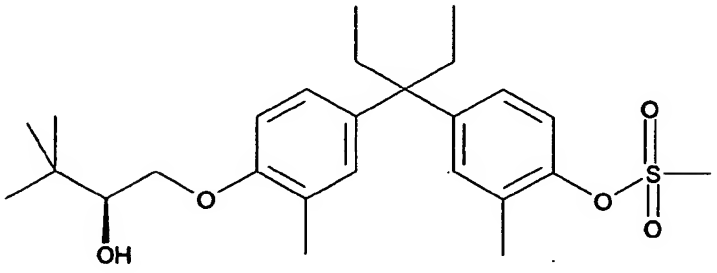


or

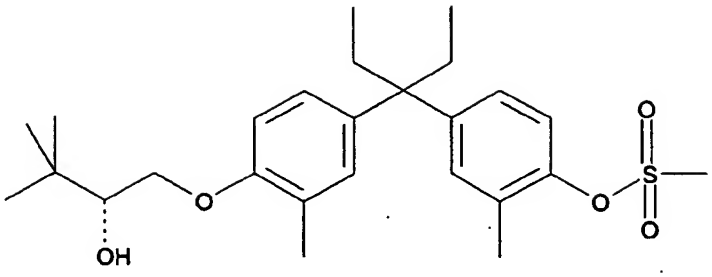
M-50)



6. The compound represented by the formula:



or



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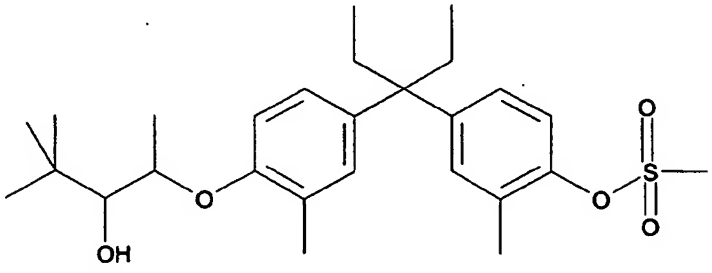

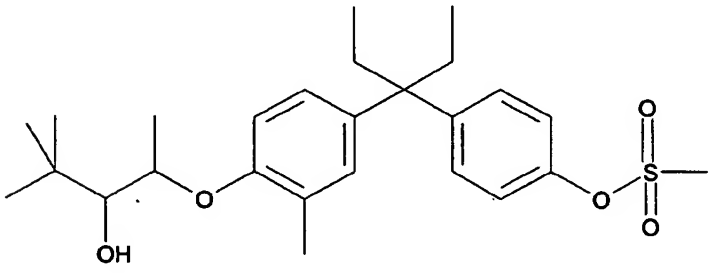

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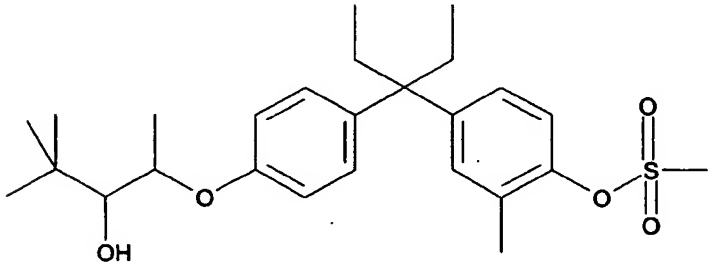

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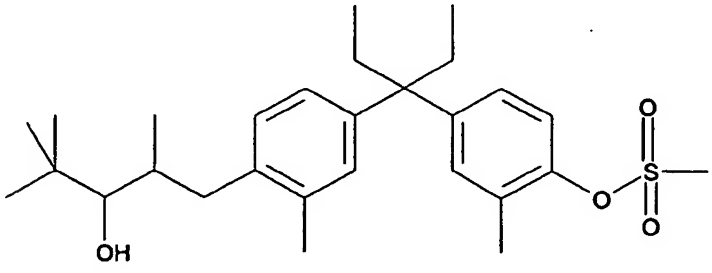

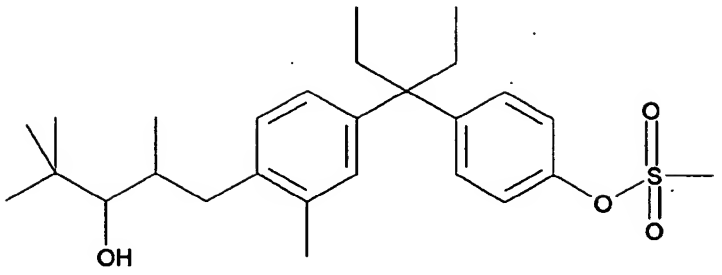

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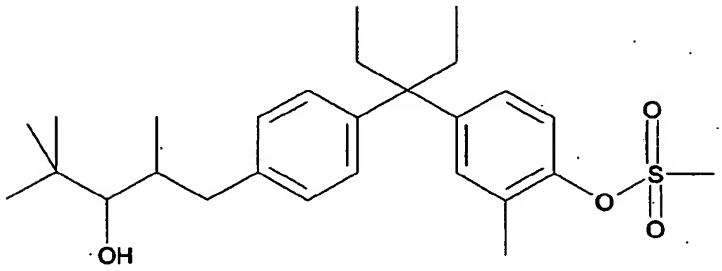

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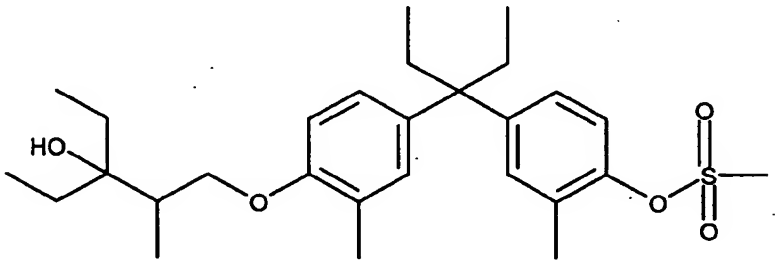

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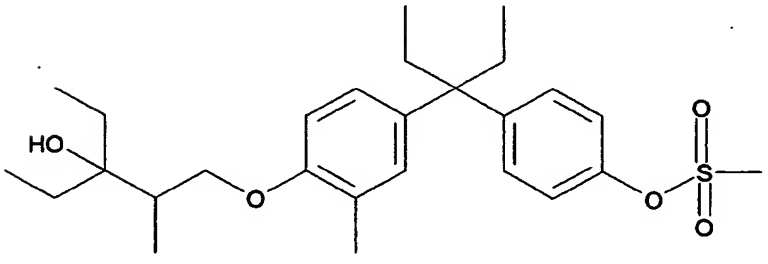

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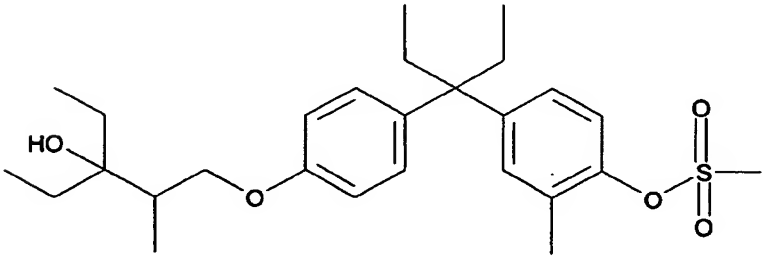

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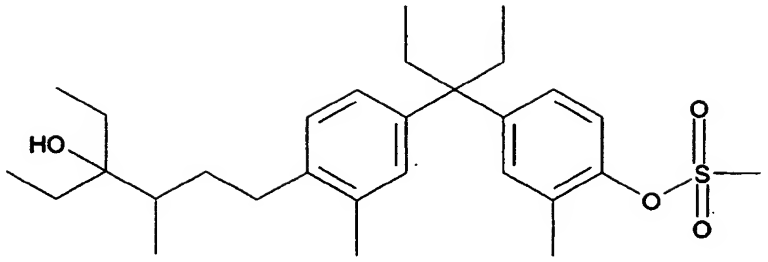
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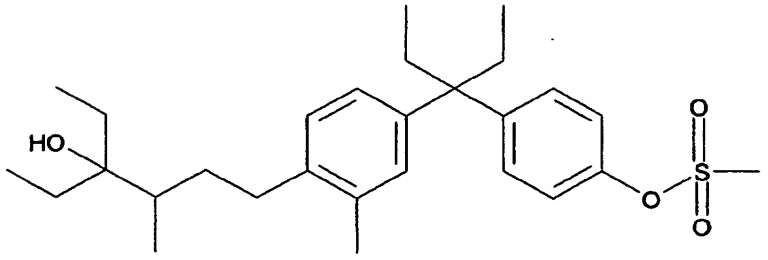
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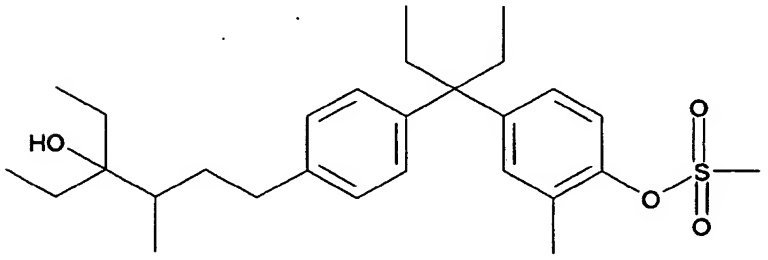
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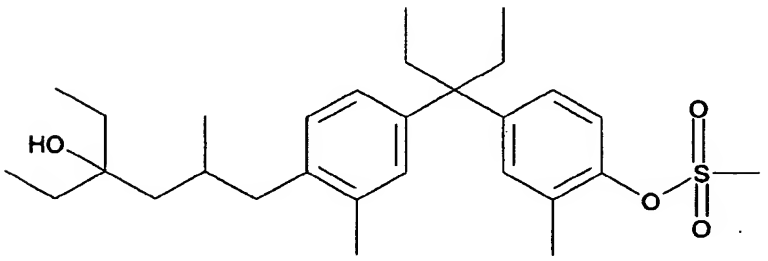
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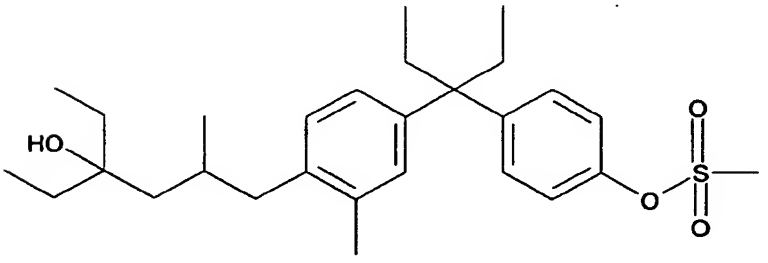
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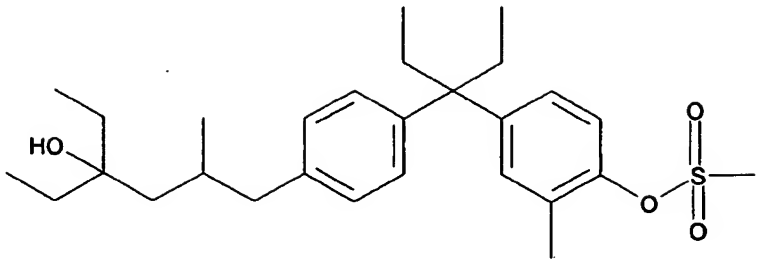

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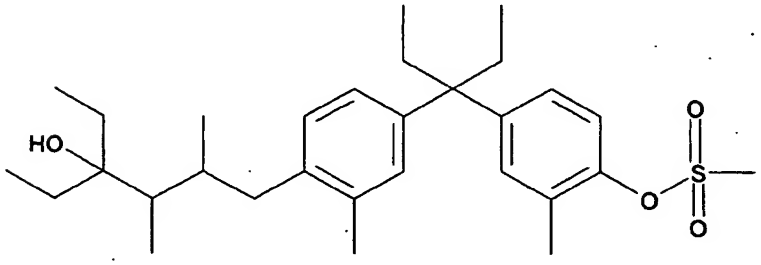

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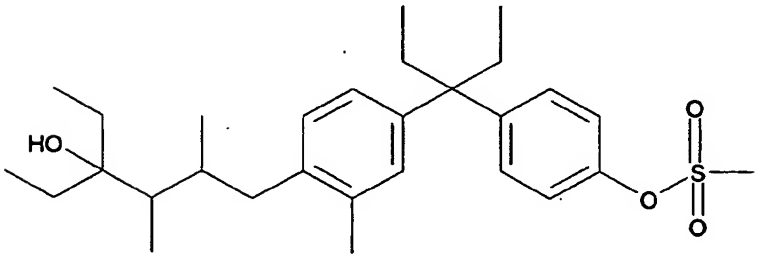

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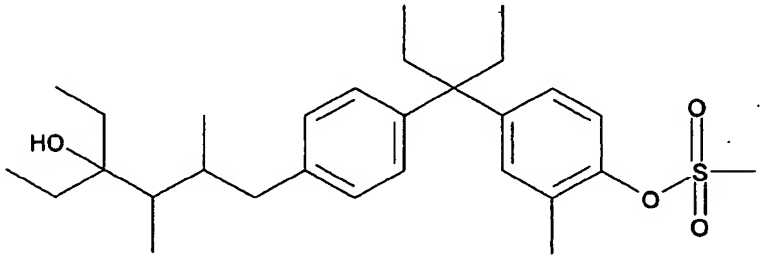
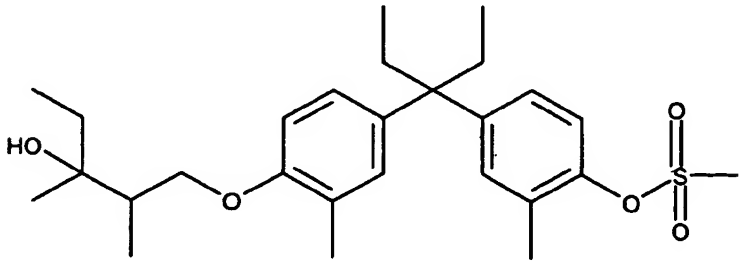


10. The compound represented by the formula:



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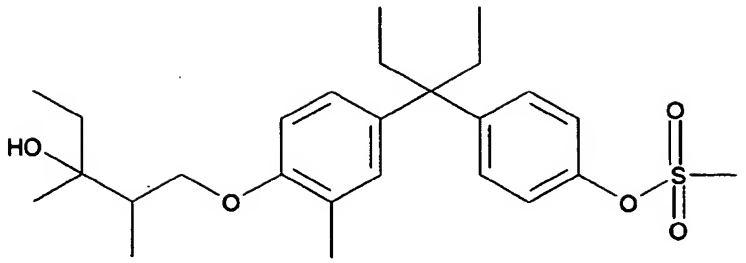
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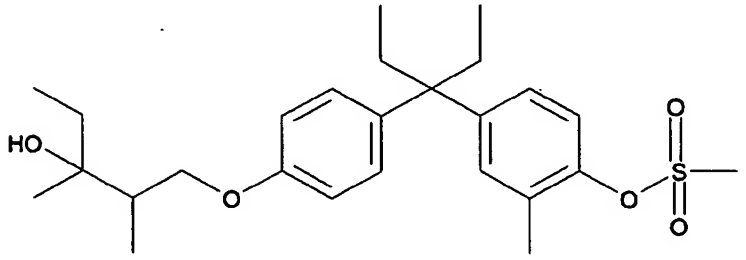
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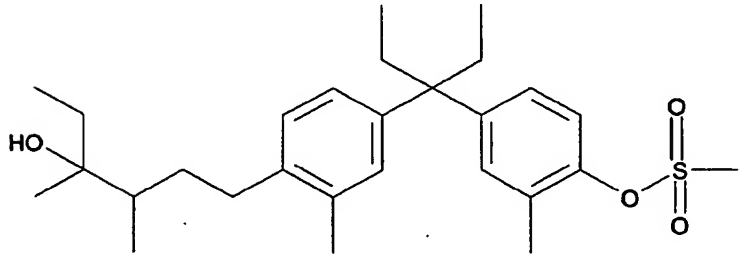
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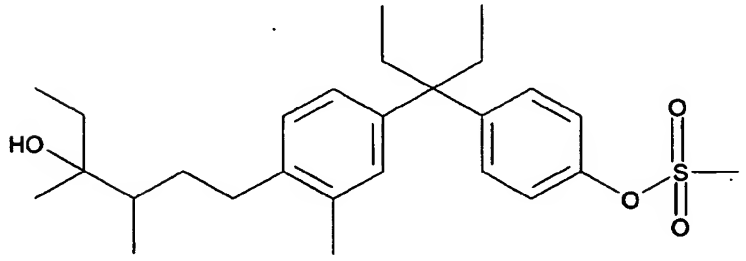
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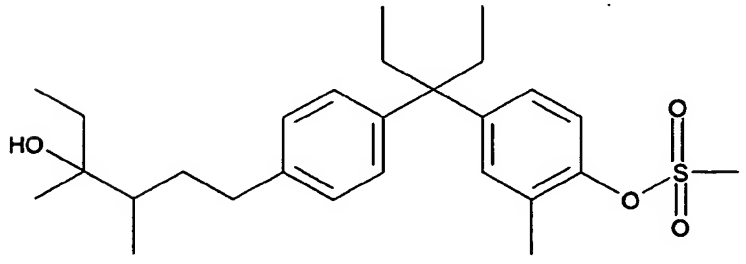
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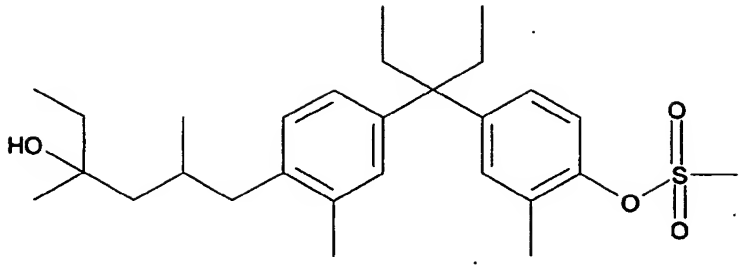

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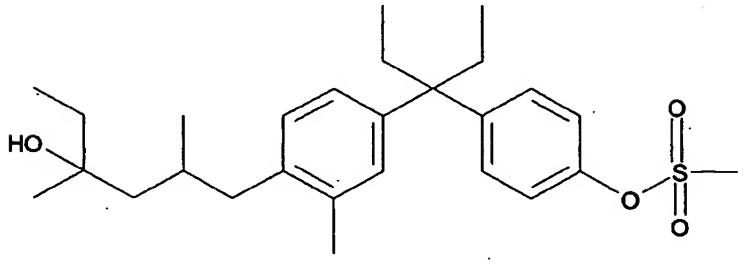

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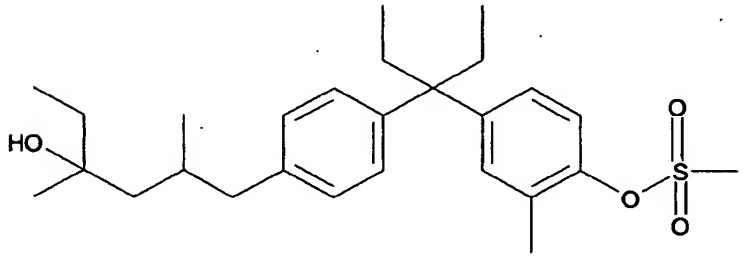

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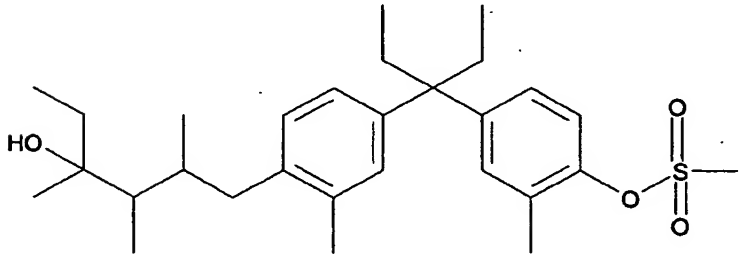

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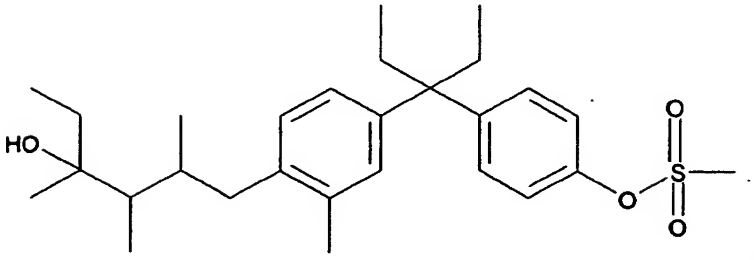

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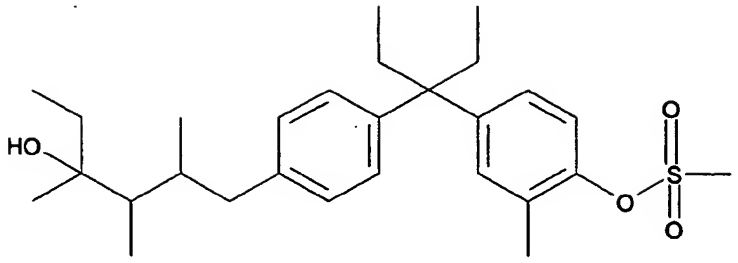
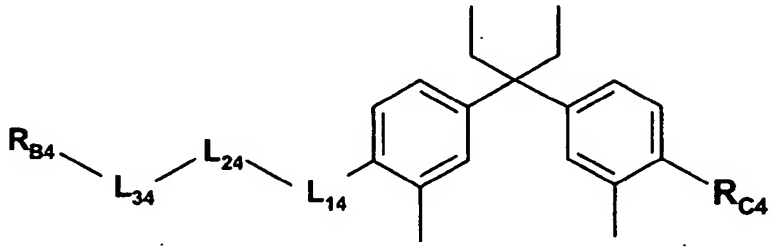


11. A compound or a pharmaceutically acceptable salt or an ester prodrug derivative thereof represented by the formula:



where said compound is selected from a compound code numbered 1 thru 135, with each compound having the specific selection of substituents R_{B4}, R_{C4}, L_{14}, L_{24}, L_{34}, and R_{C4} shown in the row following the compound code number, as set out in the following Table 1 :

Table 1

Code No.	R_{B4}	L_{34}	L_{24}	L_{14}	R_{C4}
1	tBu	C(O)	CH2	O	-O-S(O)2Me
2	tBu	C(O)	CH2	CH2	-O-S(O)2Me
3	tBu	C(O)	CH(ME)	CH2	-O-S(O)2Me
4	tBu	CHOH	CH2	O	-O-S(O)2Me
5	tBu	CHOH	CH2	CH2	-O-S(O)2Me
6	tBu	CHOH	CH(ME)	CH2	-O-S(O)2Me
7	tBu	C(Me)OH	CH2	O	-O-S(O)2Me
8	tBu	C(Me)OH	CH2	CH2	-O-S(O)2Me
9	tBu	C(Me)OH	CH(ME)	CH2	-O-S(O)2Me
10	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Me
11	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Me

12	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Me
13	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Me
14	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Me
15	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Me
16	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Me
17	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Me
18	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Me
19	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Me
20	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2Me
21	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Me
22	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Me
23	1-hydroxycyclohexy	bond	CH2	CH2	-O-S(O)2Me
24	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Me
25	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Me
26	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2Me
27	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Me
28	tBu	C(O)	CH2	O	-O-S(O)2Et
29	tBu	C(O)	CH2	CH2	-O-S(O)2Et
30	tBu	C(O)	CH(ME)	CH2	-O-S(O)2Et
31	tBu	CHOH	CH2	O	-O-S(O)2Et
32	tBu	CHOH	CH2	CH2	-O-S(O)2Et
33	tBu	CHOH	CH(ME)	CH2	-O-S(O)2Et
34	tBu	C(Me)OH	CH2	O	-O-S(O)2Et
35	tBu	C(Me)OH	CH2	CH2	-O-S(O)2Et
36	tBu	C(Me)OH	CH(ME)	CH2	-O-S(O)2Et
37	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Et
38	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Et
39	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Et
40	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Et
41	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Et
42	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Et

43	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2Et
44	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2Et
45	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2Et
46	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Et
47	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2Et
48	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Et
49	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Et
50	1-hydroxycyclohexy	bond	CH2	CH2	-O-S(O)2Et
51	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Et
52	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2Et
53	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2Et
54	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2Et
55	tBu	C(O)	CH2	O	-O-S(O)2CH2CO2H
56	tBu	C(O)	CH2	CH2	-O-S(O)2CH2CO2H
57	tBu	C(O)	CH(ME)	CH2	-O-S(O)2CH2CO2H
58	tBu	CHOH	CH2	O	-O-S(O)2CH2CO2H
59	tBu	CHOH	CH2	CH2	-O-S(O)2CH2CO2H
60	tBu	CHOH	CH(ME)	CH2	-O-S(O)2CH2CO2H
61	tBu	C(Me)OH	CH2	O	-O-S(O)2CH2CO2H
62	tBu	C(Me)OH	CH2	CH2	-O-S(O)2CH2CO2H
63	tBu	C(Me)OH	CH(ME)	CH2	-O-S(O)2CH2CO2H
64	1-hydroxycyclopentyl	bond	CH2	O	-O-

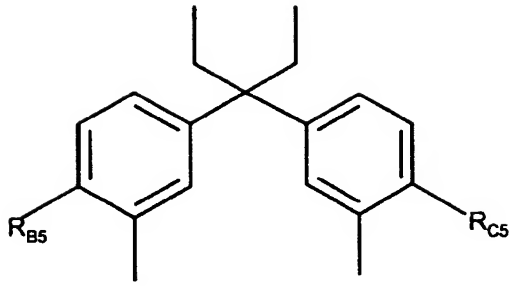
					S(O)2CH2CO2H
65	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2CH2CO2H
66	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
67	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2CH2CO2H
68	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2CH2CO2H
69	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
70	1-hydroxycyclopentyl	bond	CH2	O	-O-S(O)2CH2CO2H
71	1-hydroxycyclopentyl	bond	CH2	CH2	-O-S(O)2CH2CO2H
72	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
73	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2CH2CO2H
74	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2CH2CO2H
75	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
76	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2CH2CO2H
77	1-hydroxycyclohexy	bond	CH2	CH2	-O-S(O)2CH2CO2H
78	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
79	1-hydroxycyclohexyl	bond	CH2	O	-O-S(O)2CH2CO2H

80	1-hydroxycyclohexyl	bond	CH2	CH2	-O-S(O)2CH2CO2H
81	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-O-S(O)2CH2CO2H
82	tBu	C(O)	CH2	O	-NH-S(O)2Me
83	tBu	C(O)	CH2	CH2	-NH-S(O)2Me
84	tBu	C(O)	CH(ME)	CH2	-NH-S(O)2Me
85	tBu	CHOH	CH2	O	-NH-S(O)2Me
86	tBu	CHOH	CH2	CH2	-NH-S(O)2Me
87	tBu	CHOH	CH(ME)	CH2	-NH-S(O)2Me
88	tBu	C(Me)OH	CH2	O	-NH-S(O)2Me
89	tBu	C(Me)OH	CH2	CH2	-NH-S(O)2Me
90	tBu	C(Me)OH	CH(ME)	CH2	-NH-S(O)2Me
91	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2Me
92	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2Me
93	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2Me
94	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2Me
95	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2Me
96	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2Me
97	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2Me
98	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2Me
99	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2Me
100	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2Me
101	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2Me
102	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2Me
103	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2Me
104	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2Me
105	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2Me
106	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2Me
107	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2Me
108	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2Me

109	tBu	C(O)	CH2	O	-NH-S(O)2CH2CO2H
110	tBu	C(O)	CH2	CH2	-NH-S(O)2CH2CO2H
111	tBu	C(O)	CH(ME)	CH2	-NH-S(O)2CH2CO2H
112	tBu	CHOH	CH2	O	-NH-S(O)2CH2CO2H
113	tBu	CHOH	CH2	CH2	-NH-S(O)2CH2CO2H
114	tBu	CHOH	CH(ME)	CH2	-NH-S(O)2CH2CO2H
115	tBu	C(Me)OH	CH2	O	-NH-S(O)2CH2CO2H
116	tBu	C(Me)OH	CH2	CH2	-NH-S(O)2CH2CO2H
117	tBu	C(Me)OH	CH(ME)	CH2	-NH-S(O)2CH2CO2H
118	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2CH2CO2H
119	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
120	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H
121	1-hydroxycyclopentyl	bond	CH2	O	-NH-S(O)2CH2CO2H
122	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
123	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H
124	1-hydroxycyclopentyl	bond	CH2	O	-NH-

					S(O)2CH2CO2H
125	1-hydroxycyclopentyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
126	1-hydroxycyclopentyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H
127	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2CH2CO2H
128	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
129	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H
130	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2CH2CO2H
131	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
132	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H
133	1-hydroxycyclohexyl	bond	CH2	O	-NH-S(O)2CH2CO2H
134	1-hydroxycyclohexyl	bond	CH2	CH2	-NH-S(O)2CH2CO2H
135	1-hydroxycyclohexyl	bond	CH(ME)	CH2	-NH-S(O)2CH2CO2H

12. A compound of the invention or a pharmaceutically acceptable salt or an ester prodrug derivative thereof represented by the formula:



where said compound is selected from a compound code numbered 1A thru 45A, with each compound having the specific selection of substituents R_{B5} and R_{C5} shown in the row following the compound code number, as set out in the following Table 2 :

Table 2

Code No.	R_{B5}	R_{C5}
1A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
2A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
3A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
4A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
5A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
6A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
7A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
8A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
9A	3Et3OH-Pentyl	-NH-S(O)2CH2CO2H
10A	3Et3OH-Pentyl	-O-S(O)2Me
11A	3Et3OH-Pentyl	-O-S(O)2Me
12A	3Et3OH-Pentyl	-O-S(O)2Me
13A	3Et3OH-Pentyl	-O-S(O)2Me
14A	3Et3OH-Pentyl	-O-S(O)2Me
15A	3Et3OH-Pentyl	-O-S(O)2Me
16A	3Et3OH-Pentyl	-O-S(O)2Me
17A	3Et3OH-Pentyl	-O-S(O)2Me
18A	3Et3OH-Pentyl	-O-S(O)2Me
19A	3Et3OH-Pentyl	-O-S(O)2Et

20A	3Et3OH-Pentyl	-O-S(O)2Et
21A	3Et3OH-Pentyl	-O-S(O)2Et
22A	3Et3OH-Pentyl	-O-S(O)2Et
23A	3Et3OH-Pentyl	-O-S(O)2Et
24A	3Et3OH-Pentyl	-O-S(O)2Et
25A	3Et3OH-Pentyl	-O-S(O)2Et
26A	3Et3OH-Pentyl	-O-S(O)2Et
27A	3Et3OH-Pentyl	-O-S(O)2Et
28A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
29A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
30A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
31A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
32A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
33A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
34A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
35A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
36A	3Et3OH-Pentyl	-O-S(O)2CH2CO2H
37A	3Et3OH-Pentyl	-NH-S(O)2Me
38A	3Et3OH-Pentyl	-NH-S(O)2Me
39A	3Et3OH-Pentyl	-NH-S(O)2Me
40A	3Et3OH-Pentyl	-NH-S(O)2Me
41A	3Et3OH-Pentyl	-NH-S(O)2Me
42A	3Et3OH-Pentyl	-NH-S(O)2Me
43A	3Et3OH-Pentyl	-NH-S(O)2Me
44A	3Et3OH-Pentyl	-NH-S(O)2Me
45A	3Et3OH-Pentyl	-NH-S(O)2Me

13. The prodrug derivative of the compound of claim 1 to 12 wherein the prodrug is a methyl ester; ethyl ester; N,N-diethylglycolamido ester; or morpholinylethyl ester.

14. The salt derivative of the compound of claim 1 to 12 wherein the salt is sodium or potassium.

15. A pharmaceutical formulation comprising the compound of claim 1 to 12 together with a pharmaceutically acceptable carrier or diluent.

16. A formulation for treating osteoporosis comprising:

Ingredient (A1): the vitamin D receptor modulator of claim 1;

Ingredient (B1):

one or more co-agents selected from the group consisting of:

a. estrogens,
b. androgens,
c. calcium supplements,
d. vitamin D metabolites,
e. thiazide diuretics,
f. calcitonin,
g. bisphosphonates,
h. SERMS, and
i. fluorides; and

Ingredient (C1): optionally, a carrier or diluent.

17. The formulation of claim 16 wherein the weight ratio of (A1) to (B1) is from 10:1 to 1:1000.

18. A formulation for treating psoriasis comprising:

Ingredient (A2): the vitamin D receptor modulator of claim 1;

Ingredient (B2):

one or more co-agents that are conventional for treatment psoriasis selected from the group consisting of:

a. topical glucocorticoids ,
b. salicylic acid,
c. crude coal tar; and

Ingredient (C2): optionally, a carrier or diluent.

19. The formulation of claim 18 wherein the weight ratio of (A2) to (B2) is from 1:10 to 1:100000.

20. A method of treating a mammal to prevent or alleviate the pathological effects of Acne, Actinic keratosis, Alopecia , Alzheimer's disease, Bone maintenance in zero gravity, Bone fracture healing, Breast cancer, Chemoprovention of Cancer, Crohn's disease, Colon cancer, Type I diabetes, Host-graft rejection, Hypercalcemia , Type II diabetes, Leukemia, Multiple sclerosis, Myelodysplastic syndrome, Insufficient sebum secretion, Osteomalacia, Osteoporosis, Insufficient dermal firmness, Insufficient dermal hydration, Psoriatic arthritis, Prostate cancer, Psoriasis, Renal osteodystrophy, Rheumatoid arthritis, Scleroderma, Skin cancer, Systemic lupus erythematosus, Skin cell damage from Mustard vesicants, Ulcerative colitis, Vitiligo, or Wrinkles; wherein the method comprises administering a pharmaceutically effective amount of at least one compound of claim 1 or 12.

21. The method of claim 20 for the treatment of psoriasis.

22. The method of claim 20 for the treatment of osteoporosis.

23. A method of claim 20 for treating a mammal to prevent or alleviate skin cell protection from Mustard vesicants.

24. A method of treating or preventing disease states mediated by the Vitamin D receptor, wherein a mammal in need thereof is administered a pharmaceutically effective amount of the compound of Claim 1 to 12.

25. A compound as claimed in any one of Claims 1 to 12 for use in treating a mammal to prevent or alleviate the pathological effects of Acne, Actinic keratosis, Alopecia , Alzheimer's disease, Bone maintenance in zero gravity, Bone fracture healing, Breast cancer, Chemoprovention of Cancer, Crohn's disease,

Colon cancer, Type I diabetes, Host-graft rejection, Hypercalcemia , Type II diabetes, Leukemia, Multiple sclerosis, Myelodysplastic syndrome, Insufficient sebum secretion, Osteomalacia, Osteoporosis, Insufficient dermal firmness, Insufficient dermal hydration, Psoriatic arthritis, Prostate cancer, Psoriasis, Renal osteodystrophy, Rheumatoid arthritis, Scleroderma, Skin cancer, Systemic lupus erythematosus, Skin cell protection from Mustard vesicants, Ulcerative colitis, Vitiligo, or Wrinkles.

26. A compound as claimed in any one of Claims 1 to 12 for use in treating or preventing disease states mediated by the Vitamin D receptor.

27. A compound as claimed in Claim 1 substantially as hereinbefore described with reference to any of the Examples.

28. A process for preparing a compound as claimed in claim 1 substantially as hereinbefore described with reference to any of the Examples.

29. The use of a compound as claimed in claim 1 substantially as herein described with reference to any of the Assays and Tables for mediating the Vitamin D receptor.

ABSTRACT

The present invention relates to novel, non-secosteroidal, sulfonate and sulfonamide functional diaryl compounds with vitamin D receptor (VDR) modulating activity that are less hypercalcemic than 1α,25 dihydroxy vitamin D3. These compounds are useful for treating bone disease and psoriasis.

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